DISSERTATION ON

A STUDY ON PROGNOSTIC IMPLICATION OF Hs-CRP IN ACUTE CORONARY SYNDROME (ACS) PATIENTS ADMITTED IN THANJAVUR MEDICAL COLLEGE & HOSPITAL (TMCH)

Dissertation Submitted To

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In partial fulfillment of the

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CERTIFICATE

This is to certify that dissertation entitled **"A STUDY ON PROGNOSTIC IMPLICATION OF Hs-CRP IN ACUTE CORONARY SYNDROME (ACS) PATIENTS ADMITTED IN THANJAVUR MEDICAL COLLEGE & HOSPITAL (TMCH)"** is the bonafide record of work done by **DR.V.GOKULAKRISHNAN** in the Department of General Medicine, Thanjavur Medical College, Thanjavur during his Post Graduate Course from 2014 – 2017. This is submitted as partial fulfillment for the requirement of M.D. Degree Examinations – Branch I (General Medicine) to be held in March 2017

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Certified that the thesis entitled "**A STUDY ON PROGNOSTIC IMPLICATION OF Hs-CRP IN ACUTE CORONARY SYNDROME (ACS) PATIENTS ADMITTED IN THANJAVUR MEDICAL COLLEGE & HOSPITAL (TMCH)"** has been carried out by **Dr.V.GOKULAKRISHNAN**, under my direct supervision and guidance. All the observations and conclusions have been made by the candidate herself and have been checked by me periodically.

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DECLARATION

I, **Dr.V.GOKULAKRISHNAN**, solemnly declare that dissertation titled **A STUDY ON PROGNOSTIC IMPLICATION OF Hs-CRP IN ACUTE CORONARY SYNDROME (ACS) PATIENTS ADMITTED IN THANJAVUR MEDICAL COLLEGE & HOSPITAL (TMCH)** is a bonafide work done by me at Thanjavur medical college& Hospital during January 2016- June 2016 under the guidance of Prof **Dr.C.GANESAN M.D.,** H.O.D., Department of Internal Medicine.

The dissertation is submitted to **THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSIY,** Chennai, Tamilnadu as partial fulfillment for the requirement of **M.D. Degree Examinations – Branch I (General Medicine)** to be held in March 2017.

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submitted by Dr. V. GOKULA KRISHNAN **of**

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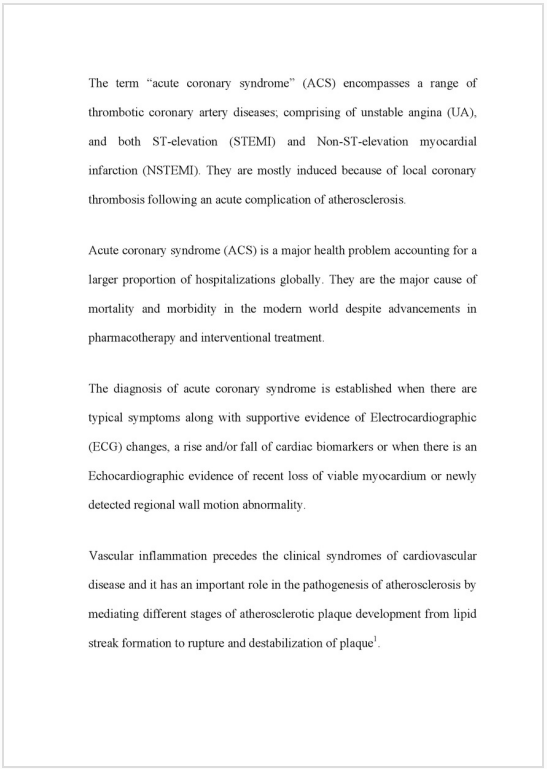
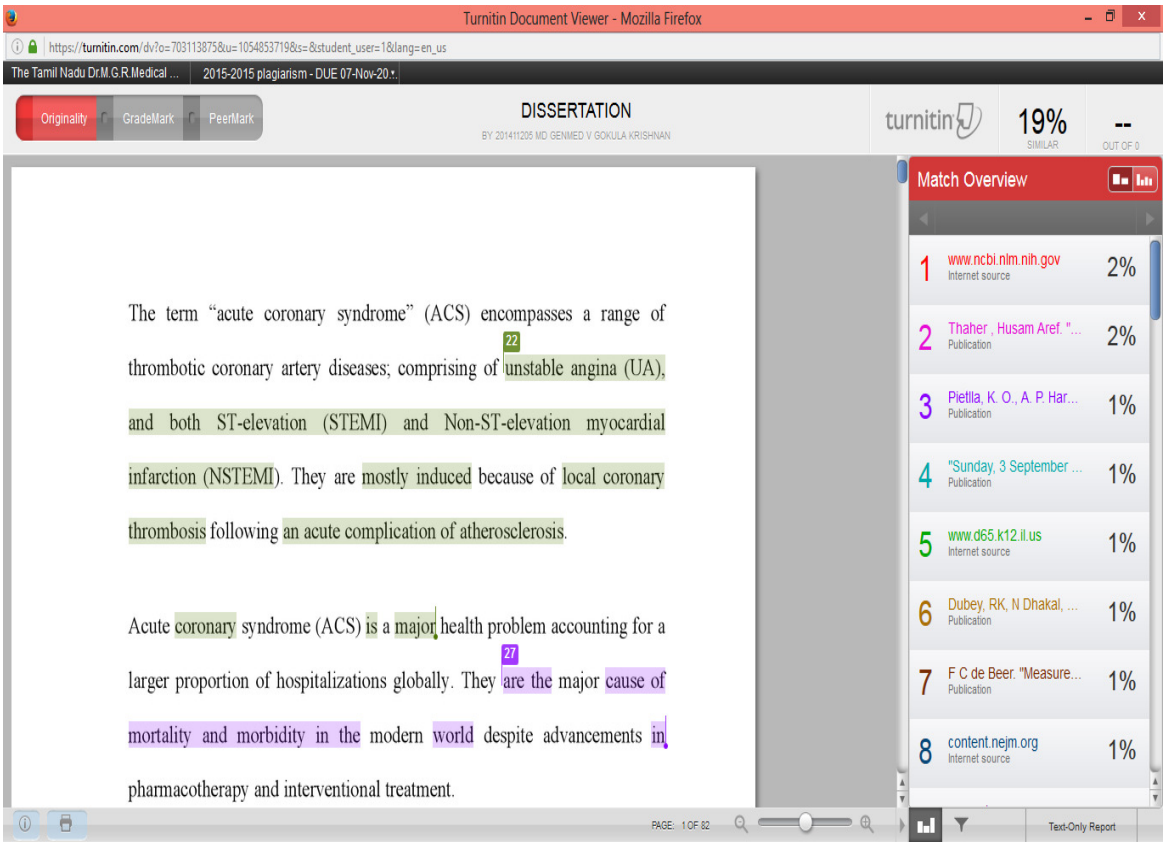


The term "acute coronary syndrome" (ACS) encompasses a range of thrombotic coronary artery diseases; comprising of unstable angina (UA), and both ST-elevation (STEMI) and Non-ST-elevation myocardial infarction (NSTEMI). They are mostly induced because of local coronary thrombosis following an acute complication of atherosclerosis.

Acute coronary syndrome (ACS) is a major health problem accounting for a larger proportion of hospitalizations globally. They are the major cause of mortality and morbidity in the modern world despite advancements in pharmacotherapy and interventional treatment.

The diagnosis of acute coronary syndrome is established when there are typical symptoms along with supportive evidence of Electrocardiographic (ECG) changes, a rise and/or fall of cardiac biomarkers or when there is an Echocardiographic evidence of recent loss of viable myocardium or newly detected regional wall motion abnormality.

Vascular inflammation precedes the clinical syndromes of cardiovascular disease and it has an important role in the pathogenesis of atherosclerosis by mediating different stages of atherosclerotic plaque development from lipid streak formation to rupture and destabilization of plaque[1].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ABBREVIATIONS

Hs -CRP – Highly sensitive C- reactive Protein

ACS- Acute Coronary Syndrome

STEMI- ST- elevation myocardial infarction

NSTEMI- Non-ST- elevation myocardial infarction

UA – unstable angina

Trop T- Troponin T

SGOT- Serum glutamic oxaloacetic transaminase

FLP- Fasting lipid profile

TC- Total Cholesterol

TGL- Triglycerides

AWMI- Anterior wall myocardial infarction

Ext. AWMI- Extensive Anterior wall myocardial infarction

ASMI- Antero septal myocardial infarction

IWMI-Inferior wall myocardial infarction

PWMI-Posterior wall myocardial infarction

RVMI- Right ventricular myocardial infarction

WP-Window period

BMI- Body Mass Index

EF- Ejection fraction

CONTENTS

The term "acute coronary syndrome" (ACS) encompasses of a range of thrombotic coronary artery diseases; comprising of unstable angina (UA), and both ST-elevation (STEMI) and Non-ST-elevation myocardial infarction (NSTEMI). They are mostly induced because of local coronary thrombosis following an acute complication of atherosclerosis.

Acute coronary syndrome (ACS) is a major health problem accounting for a larger proportion of hospitalizations globally. They are the major cause of mortality and morbidity in the modern world despite advancements in pharmacotherapy and interventional treatment.

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Vascular inflammation precedes the clinical syndromes of cardiovascular disease and it has an important role in the pathogenesis of atherosclerosis by mediating different stages of atherosclerotic plaque development from lipid streak formation to rupture and destabilization of plaque[1].

But the direct measure of this inflammatory process of atherosclerosis is complicated. Arterial biopsy to assess the coronary vessel wall alteration is neither practical nor ethical. Also, there are no imaging techniques to study the inflammatory process of atherosclerosis. Therefore, various inflammatory serum biomarkers are being assessed as potential tools for predicting acute coronary disease. These serum biomarkers of inflammation include serum amyloid A, Interleukin 6 (Il-6), fibrinogen and fibrinolytic activity, Apolipoprotein A and B100 and highly sensitive C-reactive protein (Hs-CRP)[2].

Recently, these inflammatory biomarkers have become valuable tools to study acute coronary events and the prognosis of various therapeutic interventions. *C reactive protein (CRP) estimated by high sensitivity assays, named as highly sensitive C reactive protein (Hs-CRP) is the most extensively studied serum inflammatory marker for determining acute coronary events* currently.

Several studies have reported Hs-*CRP* to have independent association with the recurrence of myocardial ischaemia and occurrence of death during follow up periods. It has been proved that CRP may not only be a biomarker of generalized inflammation but may have a direct and active role in both atherogenesis and atheromatous plaque disruption. There are certain studies

proving CRP to add independently to measures of extent and severity of coronary artery disease.

While there are several correlative studies on Hs-CRP and the coronary angiographic profile and risk factor analysis of coronary artery disease patients on long term follow up, *there are no enough published data regarding the relationship of highly sensitive C reactive protein and prognosis of coronary artery disease patients in an acute setting or on short term follow up.*

With this background, the present study was conducted to evaluate the prognostic implication of Hs-CRP in acute coronary syndrome (ACS) patients admitted in ICCU&IMCU of Thanjavur Medical College & Hospital (TMCH) during their 1 week hospital stay.

- To evaluate the prognostic implication of Hs-CRP in Acute coronary syndrome (ACS) patients admitted in Thanjavur Medical College & Hospital (TMCH).

HISTORICAL PERSPECTIVE

The body responds to injury or an infection by inflammation. Due to this inflammatory response, liver produces a protein called C-reactive protein (CRP), which is released into the blood circulation. The CRP is a plasma protein which belongs to the pentraxin family and it is the main component of any inflammatory reaction. High level of CRP is indicative of acute general inflammation of the body. The C reactive protein was first discovered at the **Rockefeller Hospital** and scientists have studied about its characteristics for about two decades to bring into medical use[3].

C-reactive protein was discovered by **Oswald T. Avery** (1877-1955) during his clinical research to develop therapy for pneumococcal pneumonia. It was named C-reactive protein as it was first found in the serum samples of patients with acute inflammatory disease, as a substance that reacted and precipitated with the pneumococcal somatic C carbohydrate antigen[4,5]. Francis and Tillett and observed that the serum samples of patients tested during the early and acute stage of pneumococcal pneumonia showed a strong precipitation reaction. But as the patient recovered the precipitation reaction diminished and eventually disappeared. They also proposed that CRP may not be a specific marker for pneumococcal infection and using Fraction C, a precipitation reaction was also found in the serum obtained

from patients with other bacterial diseases like endocarditis and acute rheumatic fever.

After several years; Avery, Theodore J. Abernethy, and Colin MacLeod (1909-1972) described many of its properties and confirmed that the C-reactive substance is a protein which is secreted by the liver[6]. Maclyn McCarty (1911-2005) crystallized CRP in his laboratory in the year 1947 and studied its level in streptococcal infections and rheumatic fever[7,8,9]. Using a test for CRP, he and his coworkers charted the course of infection in rheumatic fever patients.

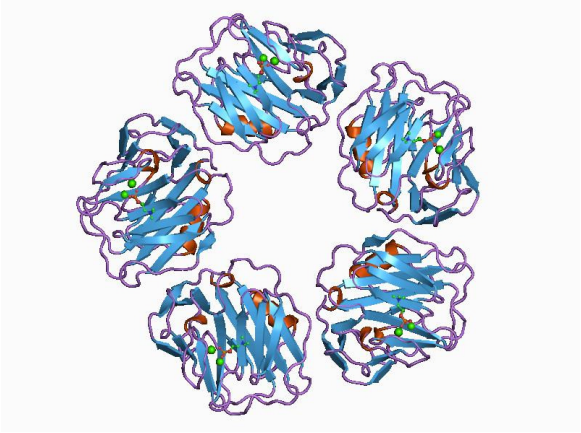
Earlier; it was hypothesised that CRP might be a secretory substance which is produced by the pathogen because it is raised in a variety of systemic illnesses, but later it was found that it is synthesized by the liver and is a native protein of the human body[6,7].

Schieffelin and Co.,which is a Newyork based company commercial manufactured CRP and introduced its widespread medical and laboratory use. In 1990, investigators recognized that inflammation contributed to the development of atherosclerosis and since then C reactive protein analysis was applied for determining cardiovascular risk.

Highly sensitive-C Reactive Protein (Hs CRP)

High-sensitivity assay techniques like immuno-nephelometry, immuno-turbidimetry, high-sensitivity enzyme-linked immune-sorbent assay (ELISA) and resonant acoustic profiling (RAP) have become available in the past decade to detect CRP[10]. These assays have a sensitivity ranging from 0.01 to 10 mg/ l. These high-sensitivity assays help to quantify low grades of systemic inflammation, even when overt systemic inflammatory or immunologic disorders are absent. Now, Hs-CRP assays have been standardised and the level of Hs CRP can be measured more accurately from fresh or frozen plasma. Recently, Hs-CRP has become the most widely evaluated inflammatory biomarker for global cardiovascular disease (CVD) risk prediction.

STUCTURE OF HUMAN C-REACTIVE PROTEIN COMPLEXED WITH PHOSPHOCHOLINE (CODE 1b09)



STUDIES ON ASSAY TECHNIQUES OF HS-CRP

Rifai N, Tracy RP, Ridker PM[11] in their comparative study (1999) on the clinical efficacy of an automated latex-enhanced assay for Hs-CRP and validated ELISA observed that for both ELISA and the Latex method, the calculated relative risks of developing peripheral arterial disease showed significant increase with every ascending quartile of Hs-CRP. The conclusion of the study was that both Latex method and validated ELISA had equal efficacy in classifying patients according to scoring established by prospective studies for risk stratification of coronary and cerebrovascular diseases.

Ahmad Hamwi, Thomas Vukovich, Oswald Wagner (2001)[12] proposed that both linear and the correlative study revealed some deficits in the performance and standardization of the Hs-CRP assay. In this study, Turbidimetric assay technique for determining Hs-CRP was observed to be more suitable for stratification of arteriosclerotic risk provided the assay is standardized and if it is possible to harmonize data from different assays by using regression equations.

Dominici R, Luraschi P and Franzini C[13] in their study (2004) compared two Hs-CRP assays, which were based on nephelometry and turbidimetry by using automated analyzers for Hs-CRP assays and observed that the two

systems performed equally in measuring Hs-CRP and CRP. But the precision of nephelometry was found to be lower than that of turbidimetry. The coefficient of variance (CV) for nephelometry was found to be 3.0-5.8 and the CV for turbidimetry was in the interval of 1.8-2.3 in this comparative study.

STUDIES ON ASSOCITION BETWEEN Hs-CRP AND ACUTE CORONARY SYNDROME

In a study conducted by de Beer FC et al[14] in 1982, the serum levels of C-reactive protein and creatine kinase-MB were estimated in confirmed cases of myocardial infarction, in subjects with spontaneous or exercise-induced angina, in cases undergoing coronary arteriography and in individuals with non-cardiac chest pain. In all patients with infarction; CRP values were increased. A statistically significant correlation was found between the peak value of CRP and CK-MB level. In this study; it was inferred that CRP peaked at about 50 hours from the onset of pain but at that time the CK-MB which peaked after 15 hours from the onset of pain had already reached a normal level. 20 patients, who recovered had decreased CRP levels and had a normal value after 7 days from infarction. In 8 patients with death reported within 10 days of admission to hospital, the level of CRP remained elevated.

Pietilä KO et al (1996) assessed the prognostic efficacy of serum C-reactive protein in patients with acute myocardial infarction[15]. In this study, the highest levels of serum C-reactive protein were found between 48 to 96 hours after the onset of myocardial infarction. The corresponding mean CRP values for patients with occurrence of death within 3, 3-6, 6-12 and 12-24 months were 166, 136, 85 and 74mg, respectively. Among patients in whom sudden cardiac death occurred and in patients, the cause of death was because of a new myocardial infarction or due to non cardiac causes, the corresponding mean serum CRP values were 167, 64 and 48mg. The CRP levels in patients who died because of congestive heart failure and in patients who suffered sudden cardiac death showed a significant difference statistically with p-value < 0.001 from the values of individuals who survived or died because of other systemic causes. But, in this study; the highest recorded serum concentrations of creatine kinase or its MB isoenzyme were not associated with death. So, the conclusion of the study was that elevated serum C-reactive protein level in AMI patients treated with thrombolytic drugs is a predictor of increased mortality rate following 6 months of myocardial infarction and a planned thrombolytic therapy may contribute to the survival benefit of acute myocardial infarction in these patients by reducing the inflammatory reaction.

In a study conducted by F. Mach[16] in 1997 on C-reactive protein as an inflammatory marker for acute coronary syndrome, the concentration of C-reactive protein was elevated in 59% of the patients with acute myocardial infarction and in 5% of the patients with unstable angina. It was concluded that in patients with myocardial infarction; the assessment of C-reactive protein at the time of admission to the hospital may lead to an improved management of myocardial infarction resulting in good prognosis and may also contribute to decreased treatment delay.

In a study conducted by Anzai T et al (1997) the serum levels of CRP were estimated 24 hourly in two hundred and twenty patients with a first Q-wave aute myocardial infarction.[17] On multivariate analysis; an increase in the peak CRP level $\geq$ 20 mg/dL was found to predict cardiac rupture, left ventricular aneurysm and cardiac death at 1 year independently, as the relative risk was calculated to be 4.72,2.11 and 3.44, respectively and the p-value were statistically significant for all the 3 variables. It was concluded that there is an association between cardiac rupture, left ventricular aneurysm and cardiac death after 1 year with elevated serum CRP level which is estimated during early hours of AMI. It was suggested that elevated CRP values following AMI may aid in predicting infarct expansion.

Oltrona L et al (1997) evaluated the prognostic importance of elevation of C reactive protein in individuals with unstable angina.[18] It was inferred that in individuals with unstable angina, the serum samples of a considerable fraction of patients showed elevated serum CRP values; but elevated concentration of CRP was not able to predict acute cardiac event in the early period of unstable angina.

Morrow DA et al (1998) evaluated serum C reactive protein separately and by combining with Troponin T in predicting the 14th day mortality rate in individuals with unstable angina and in patients with non Q wave MI.[19] It was found that in individuals who reported of a -ve troponin T, higher death rate was found in those individuals with serum C reactive protein greater than or equal to 1.55 mg/dl. Individuals who had both early +ve cardiac troponin T lesser than or equal to10 minutes and serum C reactive protein greater than or equal to 1.55 mg/dl had higher incidence of death followed by patients who had serum C reactive protein level greater than or equal to 1.55 mg/dl or a +ve cardiac troponin T. Individuals, who had negative cardiac troponin T and CRP level lesser than 1.55 mg/dl were at very low risk. It was concluded that elevated level of CRP at presentation in patients with unstable angina or Non Q wave MI is associated with an increase in the 14th day mortality rate, with individuals with a –ve cardiac troponin T also.

Rebuzzi AG et al (1998) evaluated the prognostic significance of serum troponin T and C reactive protein measured at the time of admission in patients with unstable angina pectoris.[20] The multivariate analysis of the study showed that Trop T and C reactive protein are associated independently with MI. The highest specificity of 92% was found for cardiac Trop T and the highest sensitivity of 87% was found for CRP. It was found that in patients with class IIIB unstable angina; serum troponin T and serum CRP had a significantly higher accuracy in assessing the prognosis than clinical symptoms and ECG findings.

Benamer H et al 1998 designed a study to evaluate the prognostic efficacy of cardiac Trop I and C reactive protein in unstable angina specifically in individuals with a confirmed diagnosis of CAD by angiogram[21]. Multivariate analysis of the study revealed that elevated cardiac Trop I assessed before 24 hrs of hospital admission predicted major adverse cardiac events independently both in unselected individuals with UA and in patients with a confirmed diagnosis of CAD by angiogram but it was not possible by CRP to predict major adverse cardiac events during the hospital stay.

Curzen NP et al (1998) conducted a study to evaluate if only one blood investigation to estimate C reactive protein or trop I or T concentrations can classify patients with UA (intractable) by correlating with the values of coronary anatomy and transient myocardial ischaemia.[22] The results of the study showed that Trop T alone was elevated in individuals with multiple vessel disease with a significant p-value and in those individuals with a transient myocardial ischaemia the p-value was < 0.05; and there the correlation between C reactive protein, Trop T or I and morphology of thrombotic lesion was insignificant.

Griselli M et al (1999) suggested that the peak serum CRP level has strong association to post-infarct mortality and morbidity.[23] C reactive protein binds to injured cells then stimulates the complement system thus mediating myocardial injury. It was demonstrated that human CRP and activation of the complement system mediate ischemic cardiac injury and they must be considered as targets of therapy in cardiac events.

De winter RJ in his study (1999) [24]observed that higher occurrence of major cardiac events was found in subjects with an elevated level of C reactive protein than in subjects with a normal level of CRP, both when Trop I was elevated or normal. It was concluded that an elevated level of CRP in patients with UA or Non Q wave MI is associated with a higher incidence of

major cardiac events before 6 months, both in patients having normal and incresed Trop I.

Ferreirós ER et al (1999) evaluated the in_hospital and 90th day values of C reactive protein of patients with UA and compared the values of CRP at admission and those of discharge with the outcome of treatment on the 90th day[25]. There was no association between CRP measured at the time of admission and treatment outcome during the hospital stay; but C reactive protein measured at the time of discharge was found to be a strongest independent marker of any adverse outcome with p-value = 0.0001. It was concluded that in unstable angina, CRP assessed at discharge is more related to later outcome when compared with CRP at admission and may have a great utility in risk stratification.

Ridker PM (2000)[26] conducted a case-control study in 28 thousand 2 hundred and sixty three healthy postmenopausal females for a mean follow-up period of three years to evaluate the association of risk of coronary events with baseline values of inflammatory biomarkers. Out of the 2 inflammatory biomarkers evaluated, highly sensitive C reactive protein was found as a strong univariate predictor of cardiovascular risk with a relative risk = 4.4.

Heeschen C et al (2000) assessed the predictive power of C reactive protein and cardiac troponin T in detecting cardiac risk during six months follow - up in patients with unstable angina.[27] Troponin T was greater than 0.1 µg/l in 30 percentage of patients and CRP was greater than10 mg/L in 41percentage of individuals. In multivariate analysis, it was inferred that both CRP and TnT independently predicted mortality and myocardial infarction during six months follow up of the patients. The occurrence of re-stenosis of coronary arteries during six months of follow up was not associated with troponin T status with p-value was insignificant; but, it was related to CRP status with a significantly significant p-value. It was concluded that Trop T was capable of predicting cardiac risk during the first 72 hours of UA, whereas CRP was only able to predict cardiac risk and repeated coronary revascularization during the 6 months follow up period.

Kennon S et al (2001) designed a study to evaluate the association between C reactive protein and aspirin in unstable angina.[28] There was statistically significant relation between aspirin intake and C reactive protein in predicting death and MI during 1year follow up. It was concluded that aspirin therapy modifies the acute inflammatory response to myocardial injury and this may be the primary mechanism which is responsible for this interaction.

Cusack MR (2002) suggested that in patients with unstable angina an intra-cardiac inflammatory response occurs because of low grade necrosis of myocardium and the rupture of plaque does not contribute to the acute phase response.[29]

Zairis MN et al (2002) evaluated the association of C-reactive protein levels on admission and response to thrombolysis and thereby assessed the prognostic significance in patients with ST-segment elevation acute myocardial infarction.[30] 391 individuals who underwent thrombolytic therapy for STEMI participated in this study. It was concluded that plasma levels of CRP assessed at the time of admission may predict failure of thrombolytic therapy and has prognostic efficacy in determining cardiac events in STEMI patients during both short and long term follow up periods.

In a comparative study conducted by Ridker PM[31] in 2002 on C-reactive protein and LDL cholesterol levels in predicting first cardiovascular event a weak correlation was found with a r-value=0.08. The study suggested that the C-reactive protein strongly predicted cardiovascular events than low density lipoprotein and CRP improved the prognostic efficacy of Framingham risk score.

Lenderink T (2003) evaluated whether baseline level of cardiac troponin T and CRP in capable of predicting cardiovascular events during long term

follow up periods.[32] In this study; an increase in Trop T level was related to increased procedural risk and raised levels of CRP were associated with higher risk cardiac events subsequently. It was concluded that cardiac Troponin T was a thrombotic biomarker and CRP was an inflammatory biomarker and they are capable of independently predicting impaired outcome of treatment at a four year follow-up.

Foussas SG in the year 2005 evaluated whether an increased plasma C-reactive protein level added prognostic information to the Thrombolysis in myocardial infarction risk score (TIMI) in acute coronary syndrome patients.[33] The conclusion of the study was that the plasma CRP and TIMI risk score may be combined to assess stratification of cardiac risk patients with in acute coronary syndromes. He conducted another study in the year 2007 and found that elevated levels of cardiac Trop I and Hs-CRP are related with an independent increased risk of intravenous thrombolysis failure and 30th day cardiac death in patients who received intravenous thrombolysis in the first 6 hours of STEMI.

Prashanth Panduranga (2010) conducted a correlative study on clinical and angiographic findings in unstable angina by estimating C-reactive protein. The study was conducted in Royal Hospital, Oman.[34] It was inferred that elevated CRP, measured at the time of admission when considered as a marker of in_hospital cardiac events had a sensitivity of 72%; specificity of

88% and a positive predictive value of 85%; and when considered as a marker of significant coronary artery disease had a specificity of 83% with a positive predictive value of 85%. The conclusion of the study was CRP can be used in risk stratification of unstable angina patients independent of cardiac troponin levels and patients with elevated levels of CRP (CRP>10mg/l) should undergo coronary angiography.

RK Dubey (2013)[35] conducted a study to determine whether the serum levels of CRP are higher in patients with non ST-elevation myocardial infarction acute coronary syndrome (Group II) when compared to controls (Group I). It was found that the serum levels of CRP in controls and NSTEMI ACS patients were 3.2 ± 0.25 and 11.32 ± 2.1 mg/L, respectively and these values were significantly different from each other with p-value < 0.05. Group II showed a higher level of CRP by 253% when compared to Group I subjects. It was concluded that serum CRP levels are elevated in patients with non ST-elevation myocardial infarction acute coronary syndrome and may contribute to the inflammation and thrombosis associated with acute coronary syndrome.

Deborah B Diercks (2013) conducted a study to assess the efficacy of highly sensitive C-reactive protein in identifying an acute coronary syndrome among patients admitted in the chest pain unit.[36] It was found that the

median level of highly sensitive C reactive protein was 2.2 mg/l and 2.3 mg/l in patients with and without ACS, respectively. An independent association between Hs-CRP and the diagnosis of ACS were not found in this study. It was concluded that the assessment of Hs-CRP could not aid in detecting ACS and routine Hs-CRP measurement should not be recommended as a diagnostic tool in the CPU setting.

In 2013, Raposeiras Roubín S et al [37]conducted a study to investigate the relationship between highly sensitive C reactive protein measured at the time of admission with that measured during follow up periods after an acute coronary syndrome. 151 individuals treated in the coronary care unit for ACS participated in this study. In this study; cardiac death and myocardial re-infarction during follow-up period of 19.8 months and inter-quartile range of 16.3-23.7 months were considered as the primary end point. Based on stratification of the population done by the type of ACS and adjusted to variables including Hs-CRP, diabetes mellitus, decreased ejection fraction and GRACE risk scoring which are associated with cardiac events; Hs-CRP was found to predict follow-up outcomes independently only in NSTEMI patients with a statistically significant p-value; but not in STEMI individuals in the univariate analysis. In this study, the best cut-off level of Hs-CRP to predict follow-up outcomes was found to be 1.1mg/dl and Hs- CRP assay had a sensitivity of 77.8% and specificity of 63.2%. It

was concluded that though GRACE risk scoring is used commonly for stratification of ACS patients, the estimation of Hs-CRP level may add prognostic value in the follow-up of patients with NSTEMI.

In a study conducted by Pan HC[38] in the year 2015, the scoring of coronary severity and C reactive protein in predicting MACE in individuals with stable CAD were assessed. During 42 months of follow up, out of 181 patients, 38 patients had at least 1major adverse cardiovascular event. The results of the study revealed that patients with MACE had a considerably elevated baseline level of Hs-CRP with a statistically significant p-value. Multivariate analysis revealed that severity scoring for coronary lesion, Hs-CRP and diabetes mellitus were good predictors of major adverse cardiovascular events.

Deepak Y. Kamath et al (2015) proposed that the normal values of Hs-CRP are relatively higher in the Indian population.[39] It was suggested that larger prospective cohort studies by employing standardized Hs-CRP assays with an adequate follow up period are required for deriving a risk cut-off value of Hs-CRP for acute coronary syndrome in Indian population.

Razban MM[40] in 2016 conducted a study to determine the association of serum values of highly sensitive C reactive protein and the severity of coronary lesion. The severity of coronary lesions was evaluated based on

Gensini scoring method and the association of the severity of coronary lesions and serum levels of Hs-CRP and other risk factors were assessed. An insignificant correlation was determined between the serum levels of Hs-CRP and severity of angiographic extent of the coronary arteries. It was concluded that when the coronary inflammatory process is considered as a new risk variable, the Hs-CRP assay can help in discovering new cases of coronary lesions thereby aid in follow-up and management of the positive cases.

STUDY DESIGN

The study was designed as a prospective biochemical study. The protocol of the study was approved by the Ethical committee of Thanjavur Medical College and Hospital, affiliated to Dr. M.G.R medical university. The patients in the study group were selected according to the following inclusion and exclusion criteria:

INCLUSION CRITERION:

- Patients with both ST elevation acute coronary syndrome (STEMI) and non-ST elevation acute coronary syndrome (NSTEMI) were included in the study.

EXCLUSION CRITERIA:

- Patients with angina due to secondary causes, severe aortic valve disease and obstructive hypertrophic cardiomyopathy.
- Patients with thyroid disorders, chronic hepatic diseases, renal disorders, profound hepatic or renal dysfunction.
- Patients who had previous history of stroke, patients who suffered a cerebral event at the time of admission.
- Patients with diabetic ketoacidosis, non-ketotic hyperosmolar diabetes.

- Patients with a history of recent surgery, active infection, acute infections.
- Patients with chronic inflammatory diseases.
- Patients with body temperature greater than 37.8°C at admission.

STUDY SAMPLE

48 acute coronary syndrome patients between 25-75 years of age and of both sex, who were admitted in Thanjavur Medical College and Hospital ICCU&IMCU were included in our study. 48 age and sex matched healthy individuals with no renal, metabolic or inflammatory diseases; heart failure and recent myocardial infarction were taken as controls. A complete case history was recorded for all the patients. After completing the study proforma (Annexure:1), a written informed consent (Annexure:2) was obtained from all the patients and controls who participated in the study.

Based on the clinical presentation, ECG findings and positivity for the cardiac biomarker- Troponin -T, the diagnosis of acute coronary syndrome (ACS) was established.

The diagnosis of acute coronary syndrome required the presence of at least 2 of the following criteria (1) A history of characteristic prolonged ($\geq$ 30 min) chest pain or discomfort (2) new Q waves or new abnormal ST-T features in ECG (3) positivity for the cardiac biomarker -Troponin T.

A Cardiac ECHO was also done in all the patients diagnosed for acute coronary syndrome.

Out of the 48 acute coronary syndrome patients; 36 patients were diagnosed as ST elevation MI (STEMI) and 12 patients as non ST elevation MI (NSTEMI). Out of 36 STEMI patients; 20 patients were males and 16 patients were females. Out of 12 NSTEMI patients; 6 patients were males and 6 patients were females. All the 48 Acute Coronary Syndrome (ACS) patients underwent thrombolytic therapy and they were fully interrogated and investigated during the 1 week hospital stay.

Patients were diagnosed for STEMI when they had (a) continuous chest pain upon presentation, refractory to nitrates, and lasting ≥ 30 minutes; (b) ST-segment elevation of ≥ 0.2 mV in ≥ 2 contiguous precordial leads or ≥ 0.1 mV in ≥ 2 contiguous limb leads, or new left bundle branch block on admission electrocardiogram or (c) presentation within the first 12 hours from index pain.

Patients were diagnosed for NSTEMI when they had angina-like chest pain at rest in the previous 24 hours lasting ≥ 5 minutes, with associated ST-segment depression of ≥ 0.1 mV in ≥ 2 contiguous leads upon presentation.

7ml of venous blood samples were collected from ACS patients under aseptic conditions and the highly sensitive C reactive protein (Hs CRP) levels were estimated ***within 6 hours of admission (baseline)*** **and between** ***36-48 hours (peak value)*** **of admission**. Similarly, venous blood samples were withdrawn for age and sex matched controls. They were preserved in plastic vaccum tubes (Fig 1& 2a, b) at a temperature of 2-8˚C before being assayed. Only serum was used for analysis and serum samples were clarified by centrifuging using REMI CENTRIFUGE apparatus (Fig. 3) at 2000 rpm for15 minutes and only the clear supernatant was used for testing.

High-sensitivity CRP (HsCRP) was measured by ***BTS 350 – Bio sytems autoanalyser*** (Fig.6) and by using the kit ***QUANTIA CRP–US*** (Fig.5), which is a *quantitative turbidometric immunoassay.* QUANTIA CRP –US assay kit consists of Quantia CRP activation buffer and Quantia CRP latex reagent, which is a ready to use homogenous suspension of polystyrene latex particles coated with anti-CRP antibody. The reagents were incubated in the KEMI incubator (Fig.4) before adding them to serum samples. The estimation of Hs-CRP was done at room temperature and the Quantia CRP UV calibrator was used to read the absorbance at the end of 5 minutes.

QUANTIA CRP –US is an ultrasensitive assay which provides excellent precision and the coefficient of variation was reported to be 1.77 % for a mean value of 1.64 mg/dl and 2.08 for a mean value of 0.55 mg/dl by the manafacturer. The normal range of Hs-CRP is < 0.2mg/dl as per this immuno_turbidometric assay technique.

Fasting venous blood samples taken from ACS patients were also assessed for total cholesterol (TC) and Triglycerides (TGL) by an enzymatic colorimetric assay technique. The SGOT levels were also measured. The prognosis of our patients was monitored following thrombolysis during their hospital stay.

Fig.1: ARMAMENTARIUM FOR WITHDRAWING VENOUS BLOOD

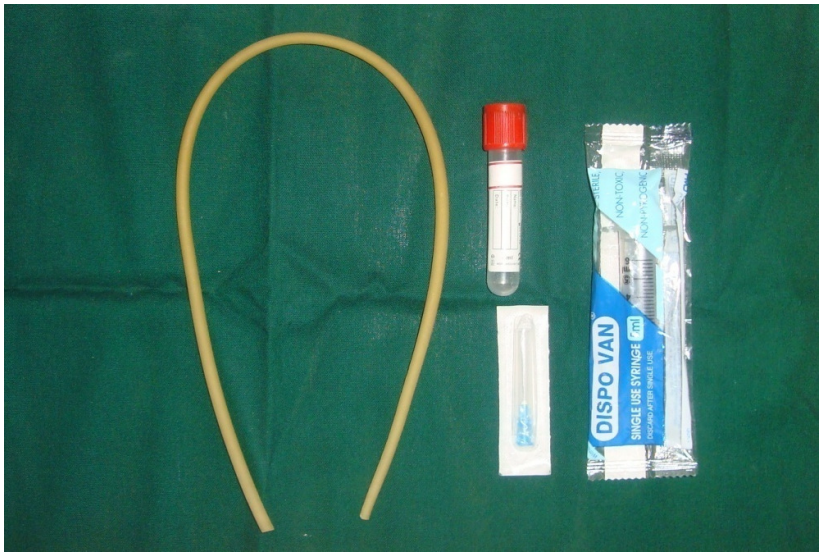


Fig.2: VENIPUNCTURE OF THE BRACHIAL VEIN AND WITHDRAWN BLOOD PRESERVED IN VACCUM TUBE

Fig 2a

Fig 2b

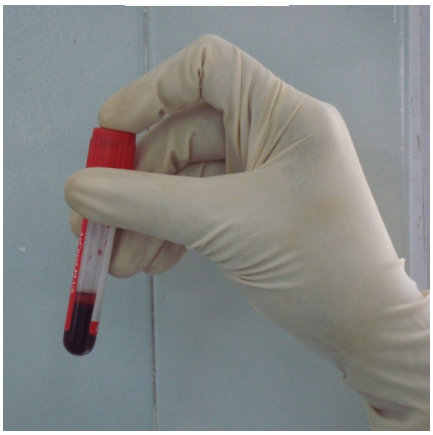


Fig. 3: CENTRIFUGING APPARATUS USED FOR OBTAINING CLEAR SUPERNATANT SERUM

Fig.4: KEMI INCUBATOR

Fig.5: QUANTIA CRP –US TURBIDOMETRIC IMMUNO ASSAY KIT

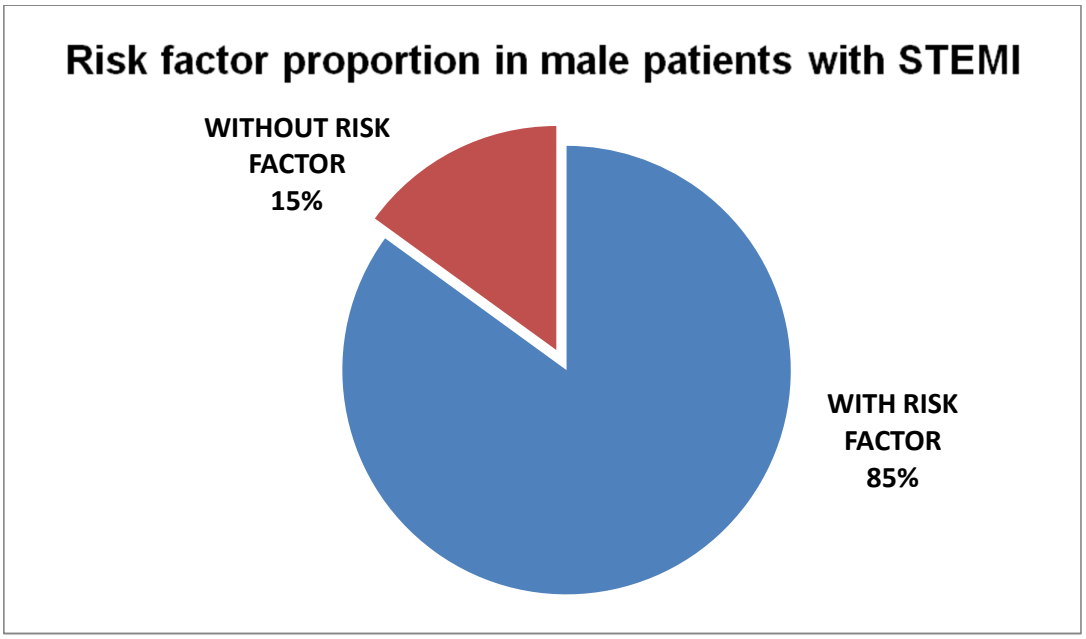
Fig.6: BTS 350 – BIO SYTEMS AUTOANALYSER

The values were tabulated and the mean of the descriptive variables of the study were calculated and the ***Pearson's correlation analysis*** was done to assess the relationship between baseline and peak values of Hs-CRP and body mass index, lipid profile and Ejection fraction.

The p-value was calculated to assess the statistical significance of relationship between the various parameters of the study. *The presence of association between the comparative variables of the study was considered to be statistically significant when the p-value was less than 0.05.*

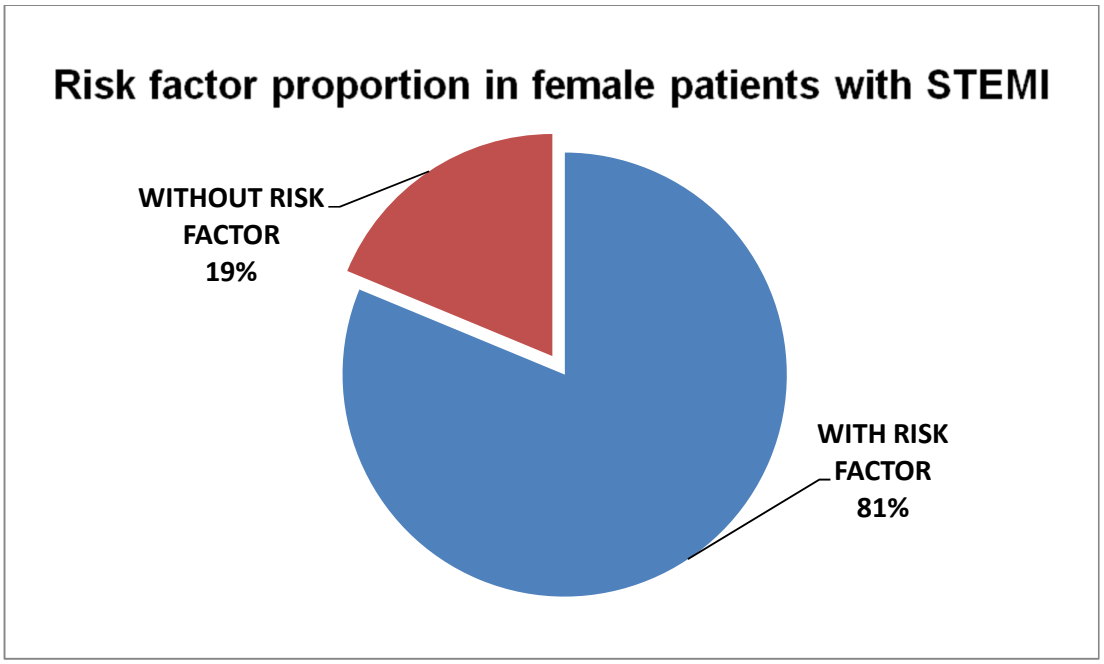
DESCRIPTIVE STATISTICS OF THE VARIABLES OF THE STUDY

VARIABLE	Group	N	MEAN	STD. DEVIATION
FLP-TC	STEMI	36	175.22	47.358
	NSTEMI	12	150.75	35.376
FLP-TGL	STEMI	36	124.53	46.805
	NSTEMI	12	125.08	38.691
Hs- CRP 6 hrs (BASELINE VALUE)	STEMI	36	**0.5242**	0.29049
	NSTEMI	12	**0.2908**	0.11766
Hs –CRP 36-48 hrs (PEAK VALUE)	STEMI	36	**1.8256**	0.42371
	NSTEMI	12	**0.9708**	0.17666
ECHO FINDING EJECTION FRACTION	STEMI	36	41.72	11.515
	NSTEMI	12	45.08	5.961



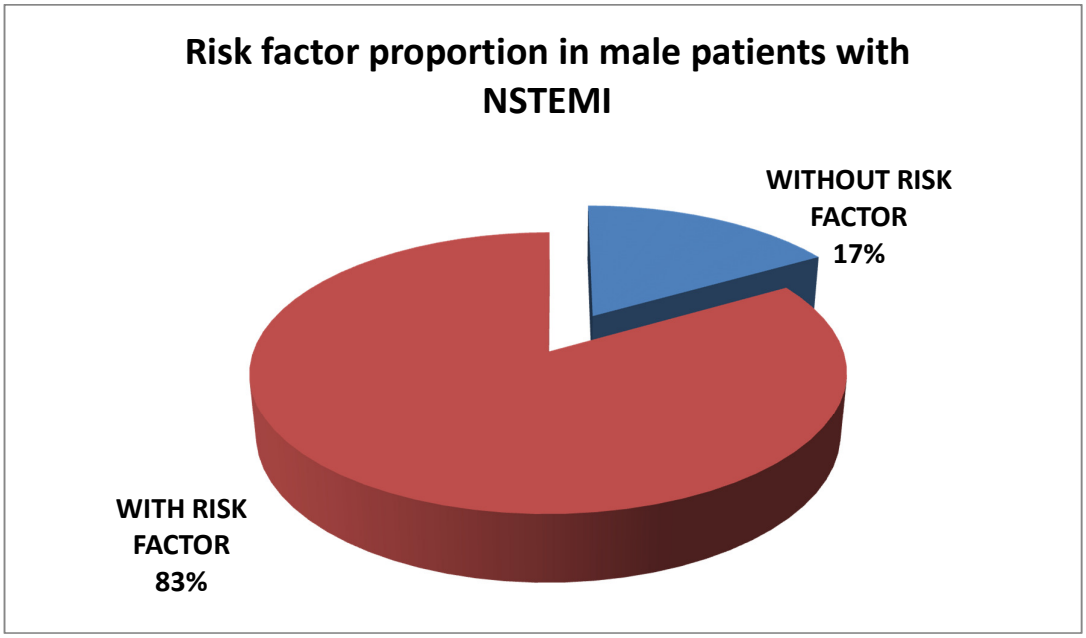
INFERENCE:

Among male patients with STEMI; **85%** of patients had risk factor of smoking, alcohol, Diabetes mellitus or Systemic Hypertension and 15% of patients had no associated risk factor.



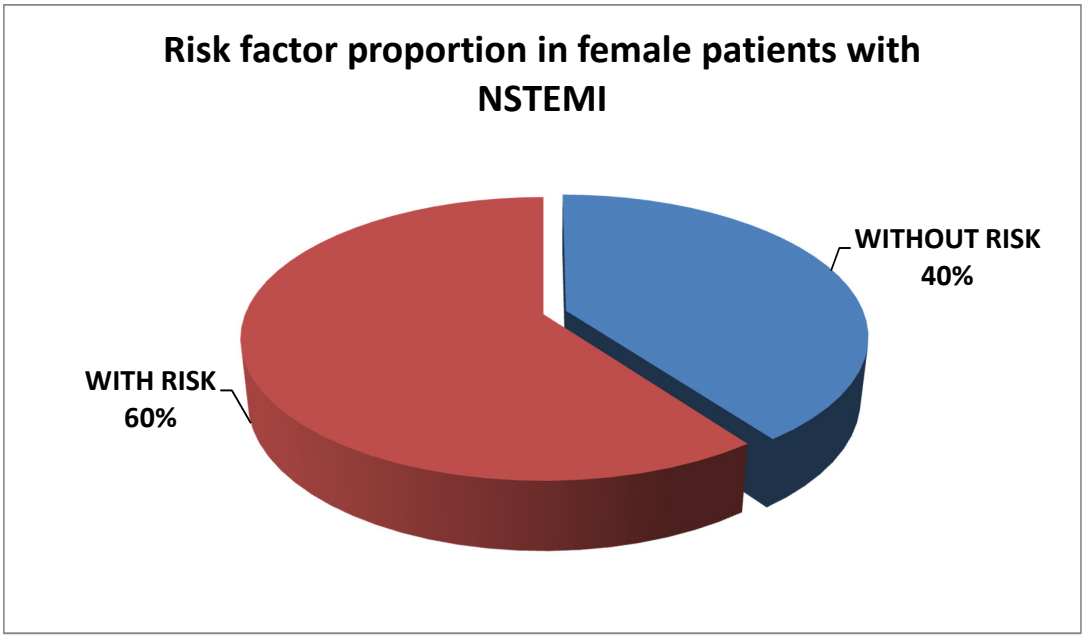
INFERENCE:

Among female patients with STEMI; **81%** of patients had risk factor of Diabetes mellitus or Systemic Hypertension and 15% of patients had no associated risk factor.



INFERENCE:

Among male patients with NSTEMI; **83%** of patients had risk factor of smoking, alcoholic, Diabetes mellitus or Systemic Hypertension and 17% of patients had no associated risk factor.



INFERENCE:

Among female patients with NSTEMI; **60%** of patients had risk factor of Diabetes mellitus or Systemic Hypertension and 40% of patients had no associated risk factor.

DESCRIPTIVE VALUES OF PEAK VALUES OF HSCRP ACCORDING TO GENDER AND TYPE OF MI

GROUP	SEX	TYPE OF STEMI	N	MEAN	STD. DEVIATION
STEMI	**Male**	1-AWMI	6	1.128	0.300
		2-EXT. AWMI	3	1.297	0.254
		3-IWMI	8	0.946	0.260
		4-ASMI	2	0.960	0.014
		5-AWMI/PWMI	2	0.960	
	Female	1-AWMI	3	1.380	0.632
		2- EXT. AWMI	2	1.775	0.205
		3-IWMI	2	1.375	0.559
		4-ASMI	2	1.345	0.191
		5-IWMI/PWMI	5	1.208	0.409
NSTEMI	**Male**	NSTEMI	6	0.992	0.130
	Female	NSTEMI	6	0.950	0.225

INFERENCE:

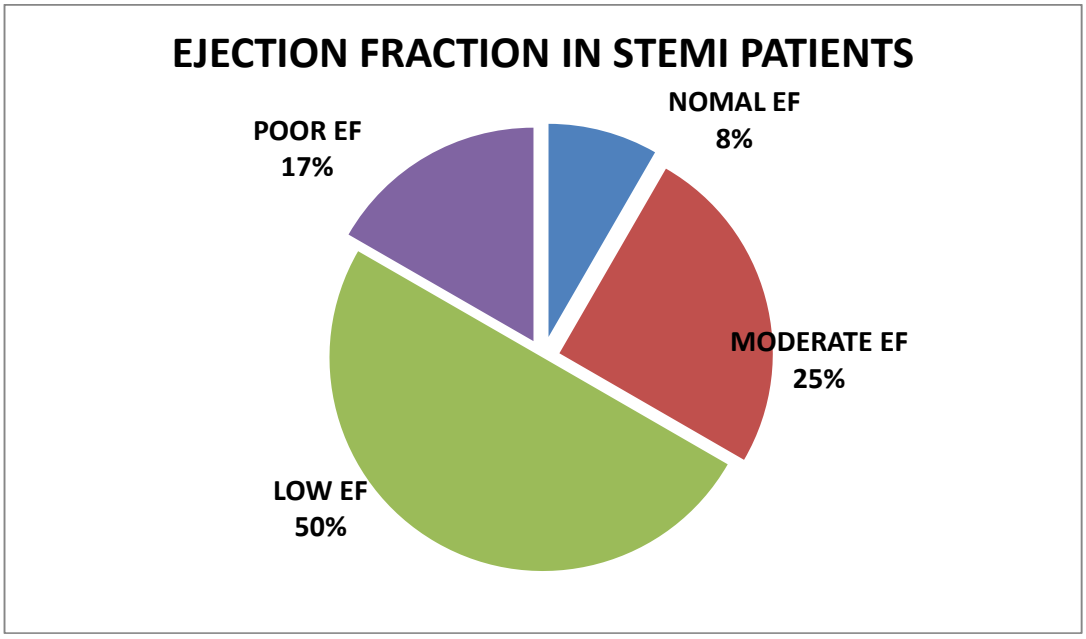
Among STEMI patients, *the highest level of peak value of Hs-CRP is seen in extensive AWMI with a mean value of* ***1.77mg/dl*** *and* ***1.29mg/dl*** *for females and males,* respectively. Among NSTEMI patients, the mean values (peak) Hs- CRP are **0.99** and **0.950** for males and females, respectively

DISTRIBUTION OF PROGNOSIS OF CASES IN MALES AND FEMALES ACCORDING TO DIFFERENT TYPES OF STEMI

SEX	PROGNOSIS	TYPE OF STEMI				
		AW MI	Ext. AWMI	IW MI	AS MI	Combination MI
Male	Death	0	1	0	0	0
	Fair	6	3	8	0	2
	Total	6	4	8		2
Female	Death	0	2	0	0	0
	Fair	3	2	2	2	5
	Total	3	4	2	2	5

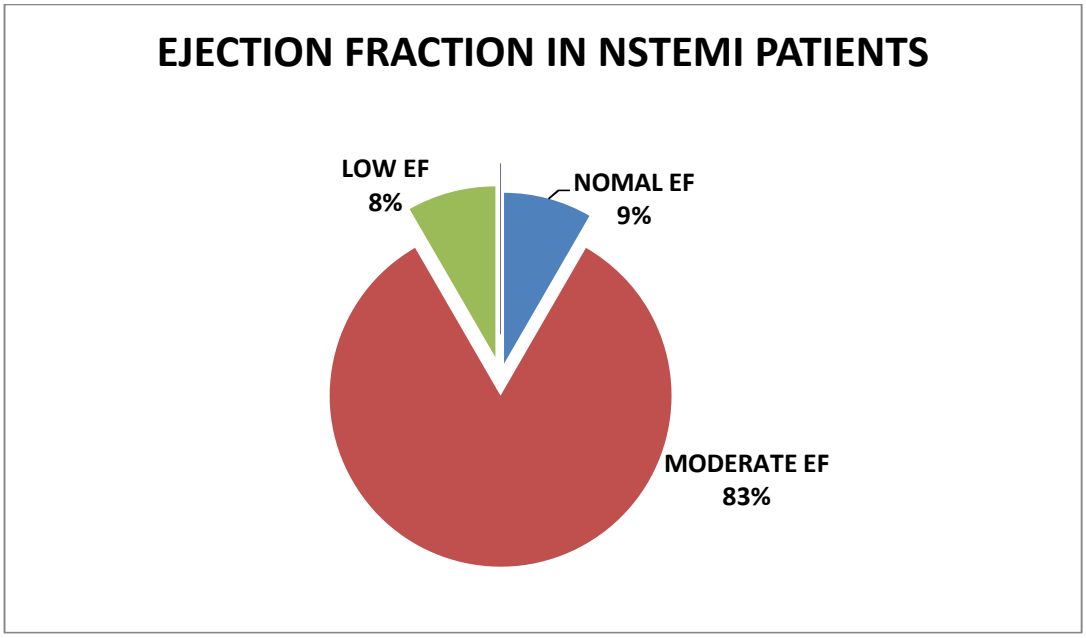
INFERENCE:

- 3 reported cases of death were there in our study and all the 3 patients had extensive anterior wall myocardial infarction.
- Out of the 3 cases; 1 was male and 2 were females.



INFERENCE:

In patients with STEMI; 8% of patients had normal EF; 25% of patients had moderate EF; 50% of patients had low EF and 17% of patients had very low Ejection fraction.



INFERENCE:

In patients with NSTEMI; 9% of patients had normal EF; 83% of patients had moderate EF; 8% of patients had low EF and no patients had very low Ejection fraction.

CORRELATION OF BASE LINE VALUES OF HS- CRP TO EJECTION FRACTION IN STEMI AND NSTEMI CASES

GROUP			EJECTION FRACTION
STEMI	Hs-CRP <6 hrs	Pearson Correlation R-value	-0.527
		P-value	.001
		N	36
NSTEMI	Hs-CRP <6 hrs	Pearson Correlation R-value	-0.213
		P-value	0.507
		N	12

INFERENCE

- ***The negative r- value is suggestive of an inverse relationship between Hs-CRP and Ejection fraction.***
- In STEMI cases, there is *good correlation with both baseline and peak values of Hs-CRP and Ejection fraction with r-value of -0.52 and - 0.65, respectively.*

- In NSTEMI cases, there is weak correlation with baseline value of Hs-CRP and ejection fraction with r value of -0.21.

CORRELATION OF PEAK VALUES OF HS CRP TO EJECTION FRACTION IN STEMI AND NSTEMI CASES

GROUP			EJECTION FRACTION
STEMI	Hs- CRP (36-48 hrs)	Pearson Correlation	-0.452
		R-value	
		P-value	.006
		N	36
NSTEMI	Hs- CRP (36-48 hrs)	Pearson Correlation	-0.540
		R-value	
		P-value	.070
		N	12

INFERENCE:

- The correlation coefficient of peak values of Hs- CRP (36-48 hrs) to ejection fraction in STEMI and NSTEMI cases are -0.65 and -0.54.

- *There is a statistically significant correlation between* peak values of Hs- CRP (36-48 hrs) to ejection fraction in STEMI patients with a p-value of 0.006

- Among **NSTEMI cases**, *the correlation between baseline and peak values of Hs-CRP and ejection fraction is statistically insignificant with p-value of 0.5 and 0.07, respectively.*

CORRELATION OF Hs- CRP TO BMI IN STEMI AND NSTEMI CASES

GROUP			BMI
STEMI	**Hs-CRP (<6 hrs)**	Pearson Correlation	0.188
		Sig. (2-tailed)	0.273
		N	36.000
	Hs- CRP (36-48 hrs)	Pearson Correlation	0.325
		Sig. (2-tailed)	0.053
		N	36.000
NSTEMI	**Hs-CRP (<6 hrs)**	Pearson Correlation	0.010
		Sig. (2-tailed)	0.975
		N	12.000
	Hs- CRP (36-48 hrs)	Pearson Correlation	0.284
		Sig. (2-tailed)	0.371
		N	12.000

INFERENCE

- *Weak correlation is present between baseline and peak values of Hs-CRP and BMI in STEMI cases.*
- *Poor strength of correlation is present between the serum levels of Hs-CRP and BMI in NSTEMI patients.*

CORRELATION OF Hs- CRP TO LIPID PROFILE IN STEMI AND NSTEMI CASES

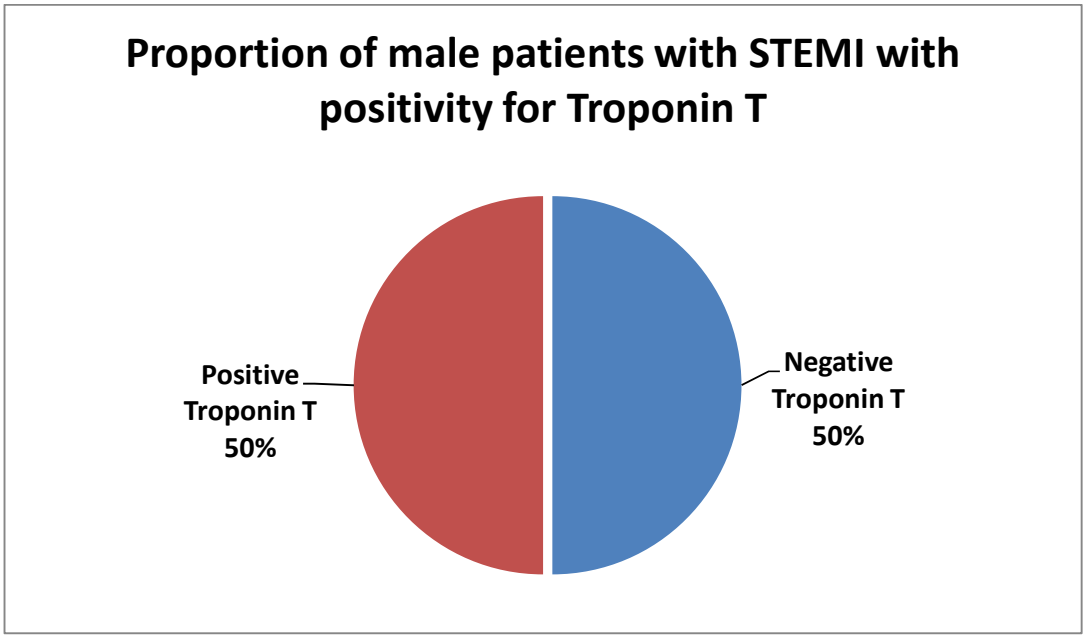
GROUP			FLP-TC	FLP-TGL
STEMI	**Hs-CRP < 6 hrs**	Pearson Correlation	-0.176	0.211
		Sig. (2-tailed)	0.303	0.217
		N	36.000	36.000
	Hs-CRP 36-48 hrs	Pearson Correlation	-0.060	0.250
		Sig. (2-tailed)	0.729	0.142
		N	36.000	36.000
NSTEMI	**Hs-CRP < 6 hrs**	Pearson Correlation	0.044	-0.546
		Sig. (2-tailed)	0.891	0.067
		N	12.000	12.000
	Hs-CRP 36-48 hrs	Pearson Correlation	0.137	-0.039
		Sig. (2-tailed)	0.672	0.903
		N	12.000	12.000

INFERENCE:

- A weak correlation exists between Hs CRP and fasting total cholesterol (FLP-TC) and triglycerides (FLP-TGL) in both STEMI

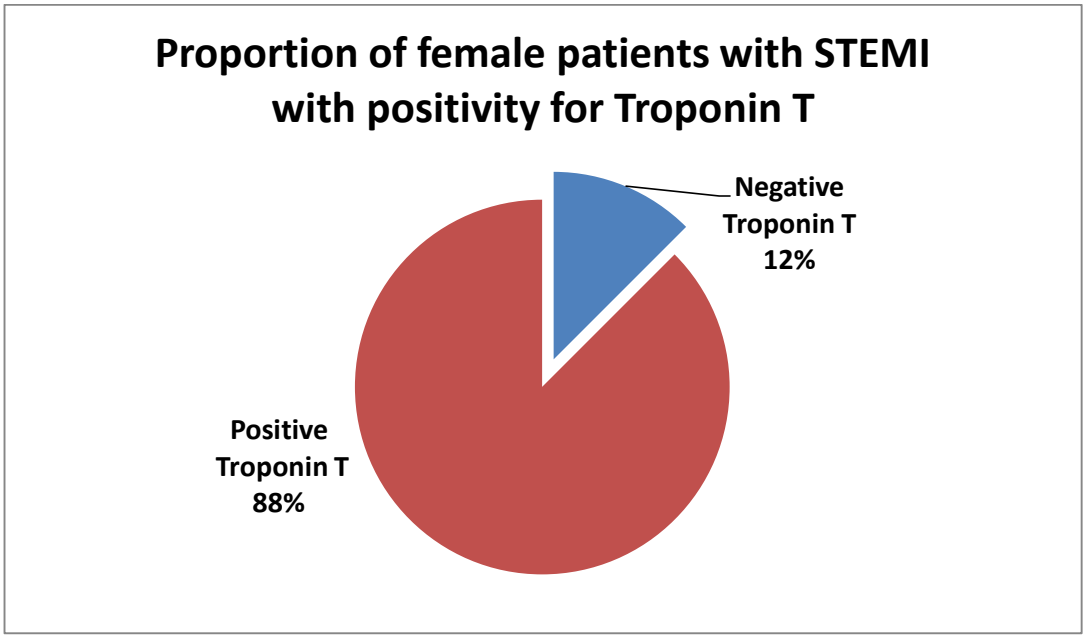
and NSTEMI cases with **r-value of -0.16 and -0.07** for TC and TGL vs baseline and peak values of Hs-CRP for STEMI patients.

- For NSTEMI patients; the r-values were **-0.04 and -0.13** for FLP-TC and FLP-TGL ,respectively vs baseline and peak values of Hs-CRP.



INFERENCE:

Among male patients with STEMI; there were *equal number of cases in positive and negative Troponin T groups*.



INFERENCE:

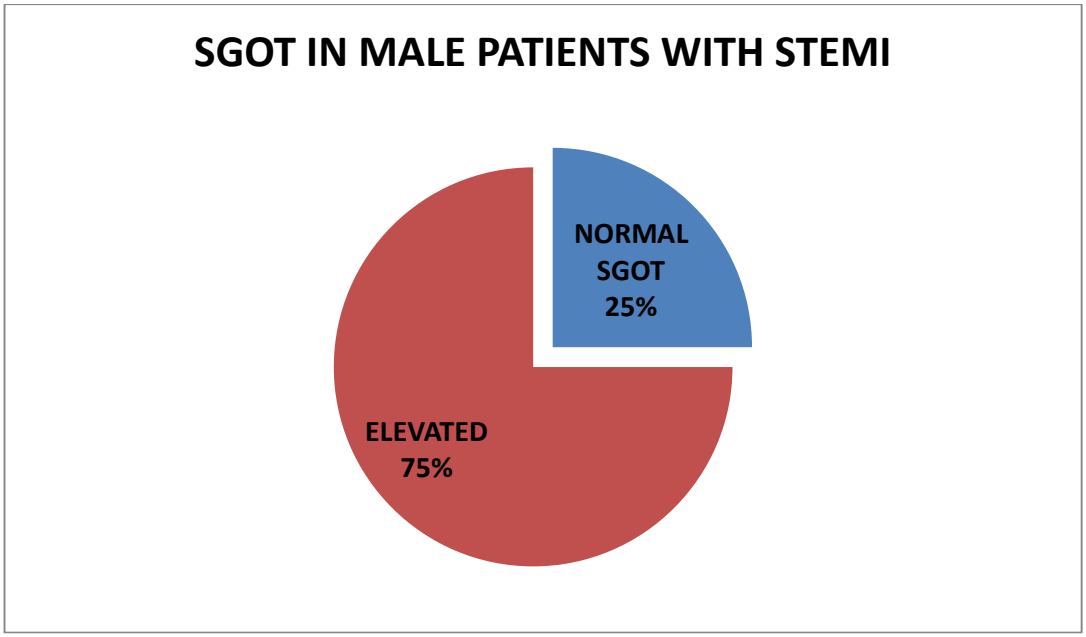
Among female patients with STEMI; *12% of patients had negative Troponin T and 88 % of patients had positive Troponin T test.*

CORRELATION OF Hs- CRP TO TROPONIN- T IN STEMI AND NSTEMI CASES

GROUP			TROPONIN- T
STEMI	**Hs-CRP < 6 hrs**	Pearson Correlation	-0.013
		Sig. (2-tailed)	0.956
		N	20.000
	Hs-CRP 36-48 hrs	Pearson Correlation	0.229
		Sig. (2-tailed)	0.332
		N	20.000
NSTEMI	**Hs-CRP < 6 hrs**	Pearson Correlation	.a
		Sig. (2-tailed)	.
		N	0.000
	Hs-CRP 36-48 hrs	Pearson Correlation	.a
		Sig. (2-tailed)	.
		N	0.000

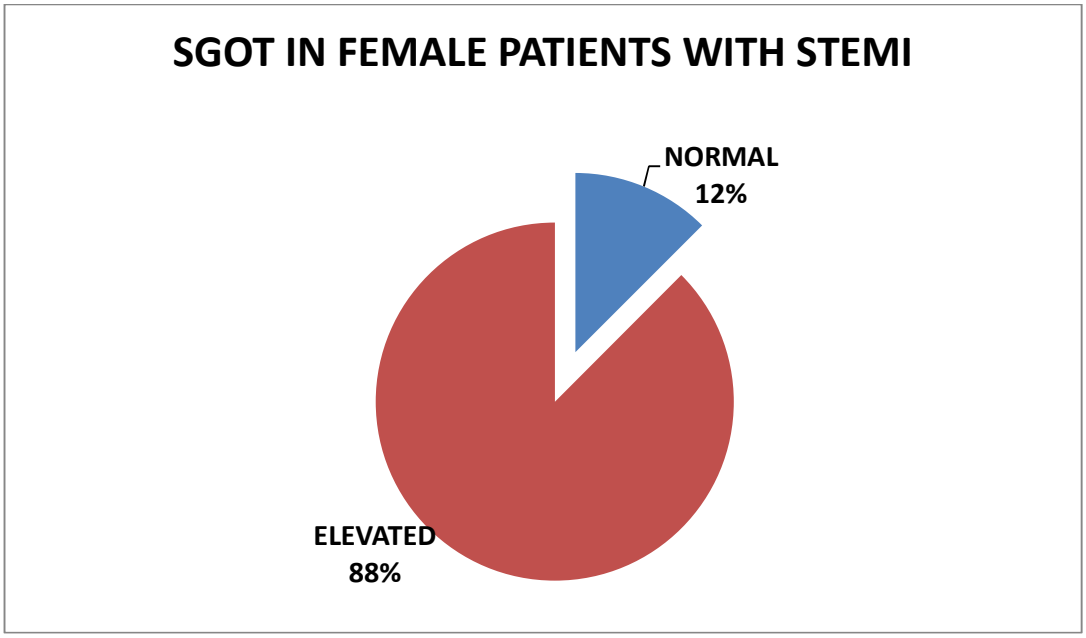
INFERENCE:

The correlation of Hs-CRP to Troponin T was statistically insignificant.



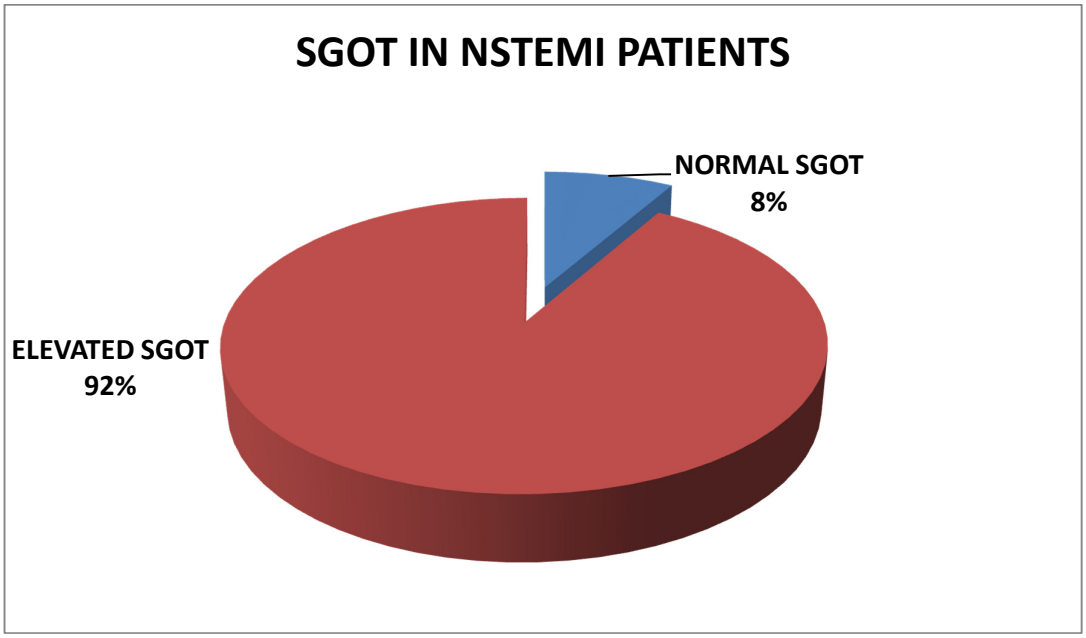
INFERENCE:

Among male patients with STEMI; 25% of patients had normal level of SGOT and 75% of patients had elevated levels of SGOT.



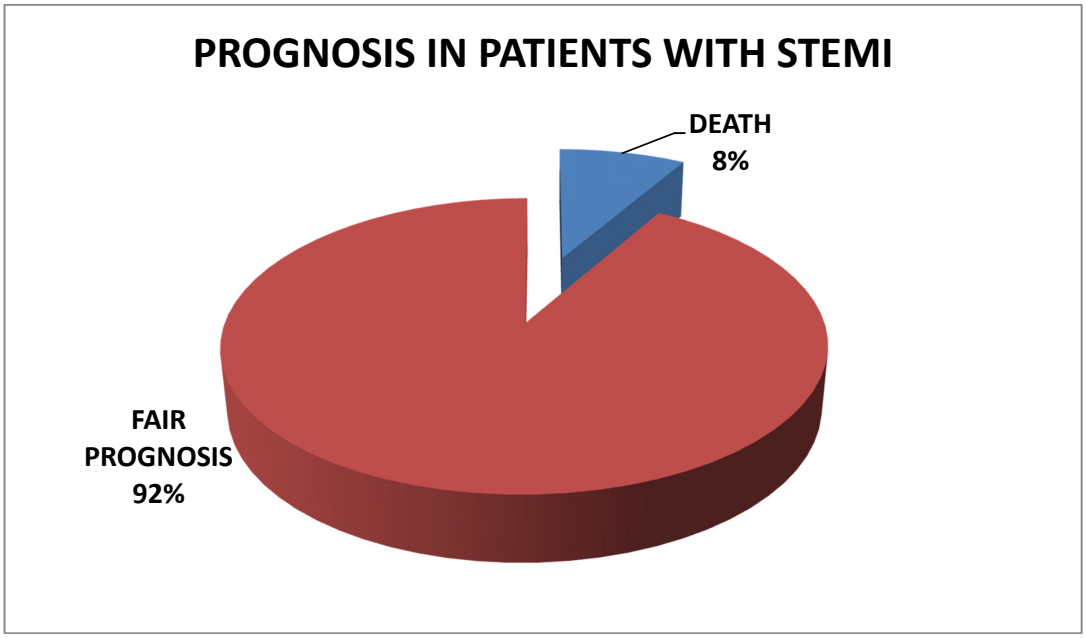
INFERENCE:

In female patients with STEMI; 12% of patients had normal level of SGOT and 88% of patients had elevated levels of SGOT.



INFERENCE:

In patients with NSTEMI; 8% of patients had normal level of SGOT and 92% of patients had elevated levels of SGOT.



INFERENCE:

In patients with STEMI; *92% of patients had fair prognosis* following thrombolytic therapy and in **8%** of patient death occurred despite thrombolytic therapy during their hospital stay.

CORRELATION OF Hs - CRP TO PROGNOSIS IN STEMI AND NSTEMI CASES

Group		Prognosis	N	Mean	Std. deviation	Mean difference	p-value
STEMI	Hs-CRP < 6 hrs	Death	3.00	1.30	0.10	0.846	<0.001
		Fair	33.00	0.45	0.17		
	Hs-CRP 36-48 hrs	Death	3.00	NA	NA	NA	NA
		Fair	33.00	1.17	0.37		
NSTEMI	Hs-CRP < 6 hrs	Death	0.00	.	.	NA	NA
		Fair	12.00	0.29	0.12		
	Hs-CRP 36-48 hrs	Death	0.00	.	.	NA	NA
		Fair	12.00	0.97	0.18		

In STEMI patients, the ***correlation between prognosis and the baseline values of Hs-CRP is statistically significant (p-value <0.05) with a p-value of 0.001.***

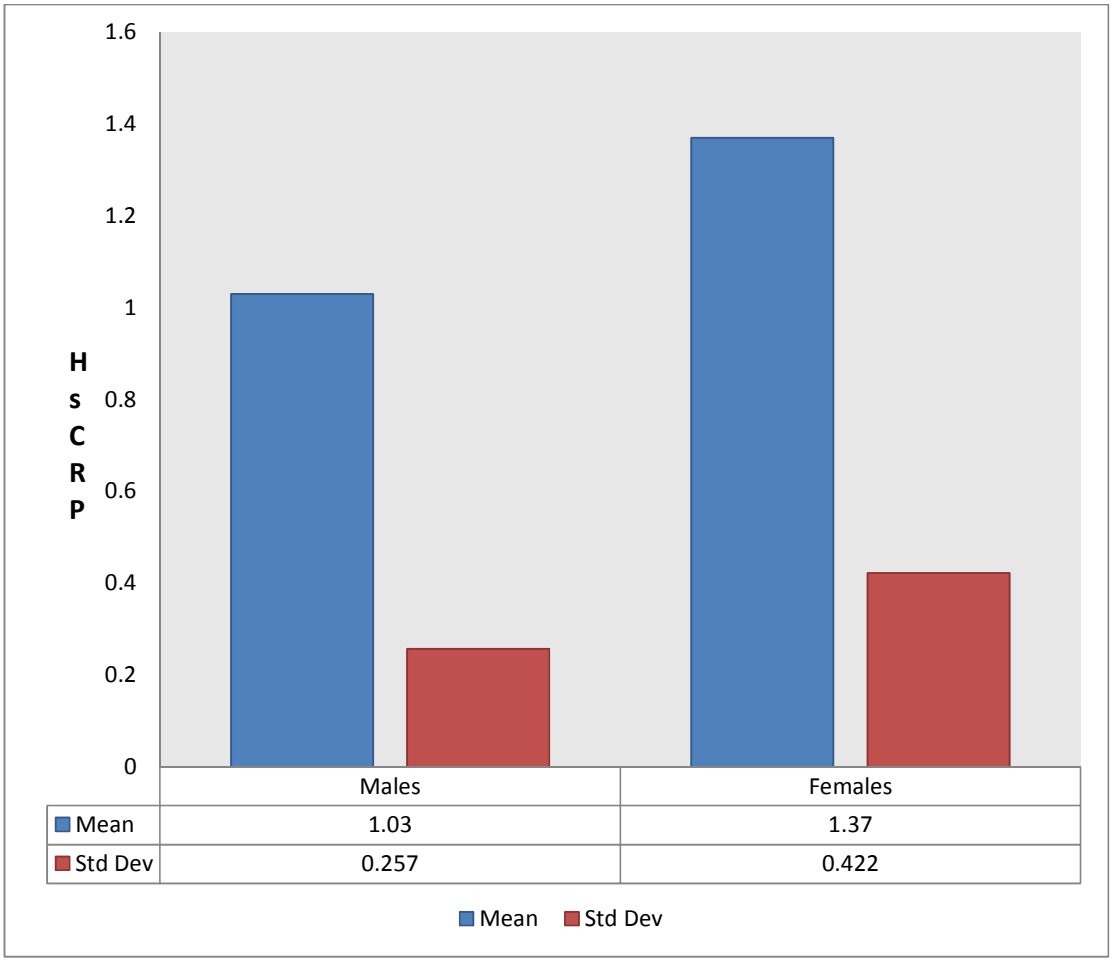
ASSOCIATION BETWEEN BASELINE VALUE OF Hs-CRP AND PROGNOSIS OF EXTENSIVE AWMI

TYPE OF STEMI		PROGNOSIS	N	Mean	Std. Deviation	Mean difference	P-value
Extensive AWMI	hscrp 6 hrs	Death	3	1.300	0.101	0.760	0.002
		Fair	5	0.540	0.227		

INFERENCE:

- The mean of baseline value of Hs-crp in patients, who faced death due to extensive AWMI is 1.33mg/dl.
- The correlation between the prognosis and baseline values of Hs-CRP of patients with extensive AWMI (among STEMI cases) is found to be statistically significant ($p < 0.05$).

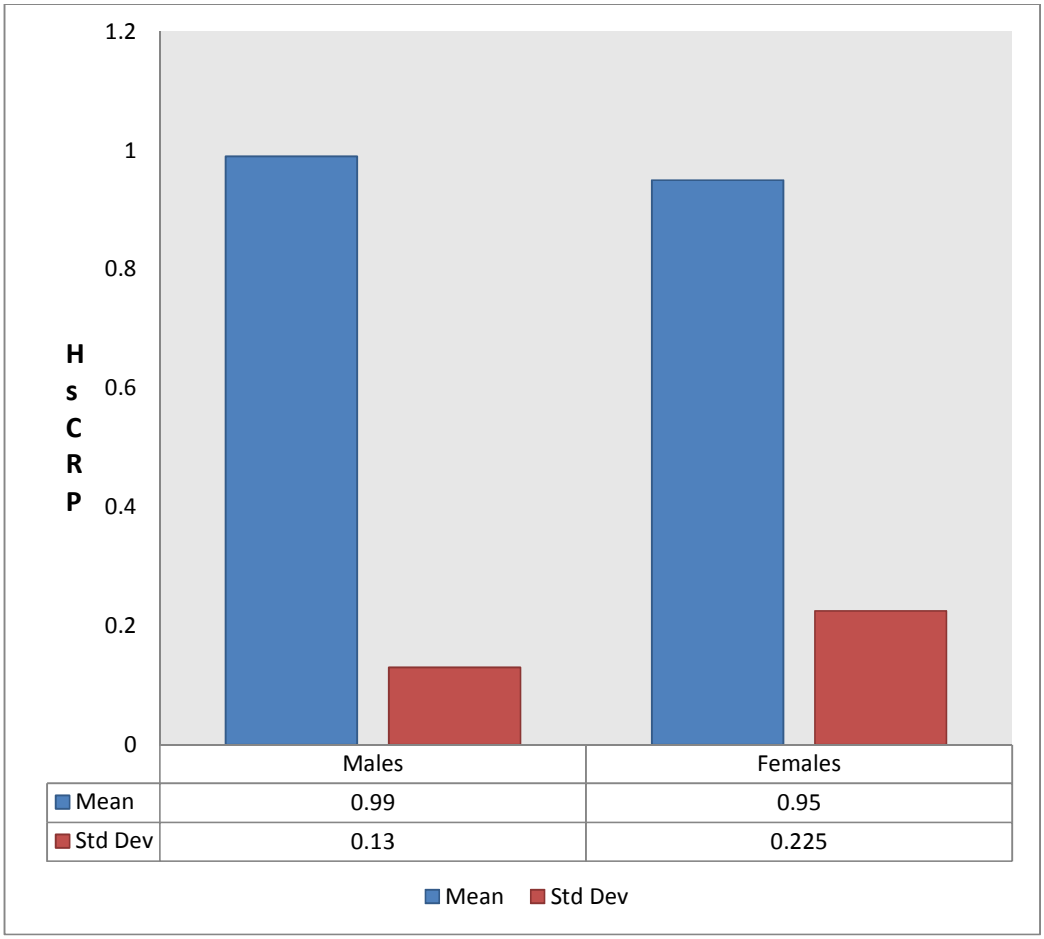
BAR DIAGRAM FOR PEAK VALUES (36-48HRS) OF Hs- CRP in MALES AND FEMALES IN STEMI PATIENTS



INFERENCE:

In *male patients with STEMI*, the mean of peak value of Hs-CRP measured between 36-48 hours was **1.03 mg/dl.** In *female patients with STEMI*, the mean of peak value of Hs-CRP measured between 36-48 hours was **1.37 mg/dl**.

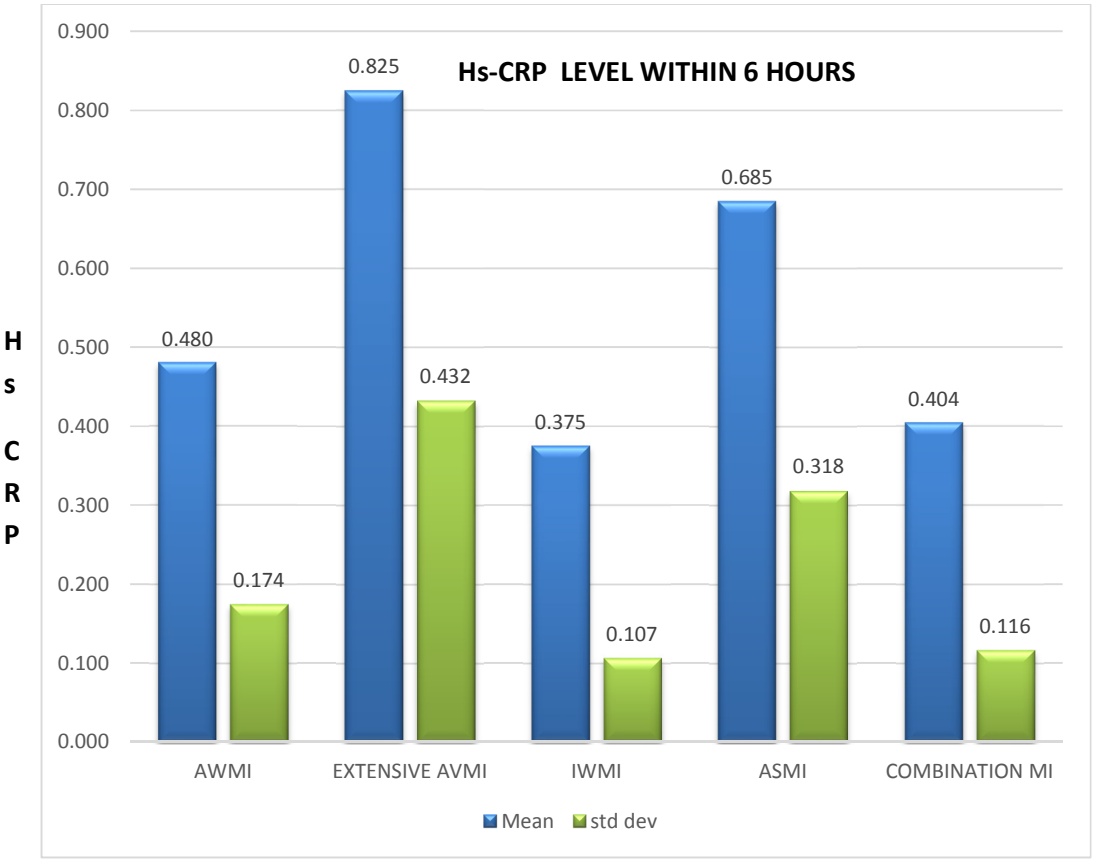
BAR DIAGRAM FOR PEAK VALUES OF Hs- CRP in MALES AND FEMALES IN NSTEMI PATIENTS



INFERENCE:

In *male patients with NSTEMI*, the mean of peak value of Hs-CRP measured between 36-48 hours was **0.99 mg/dl**. In *female patients with NSTEMI*, the mean of peak value of Hs-CRP measured between 36-48 hours was **0.95 mg/dl.**

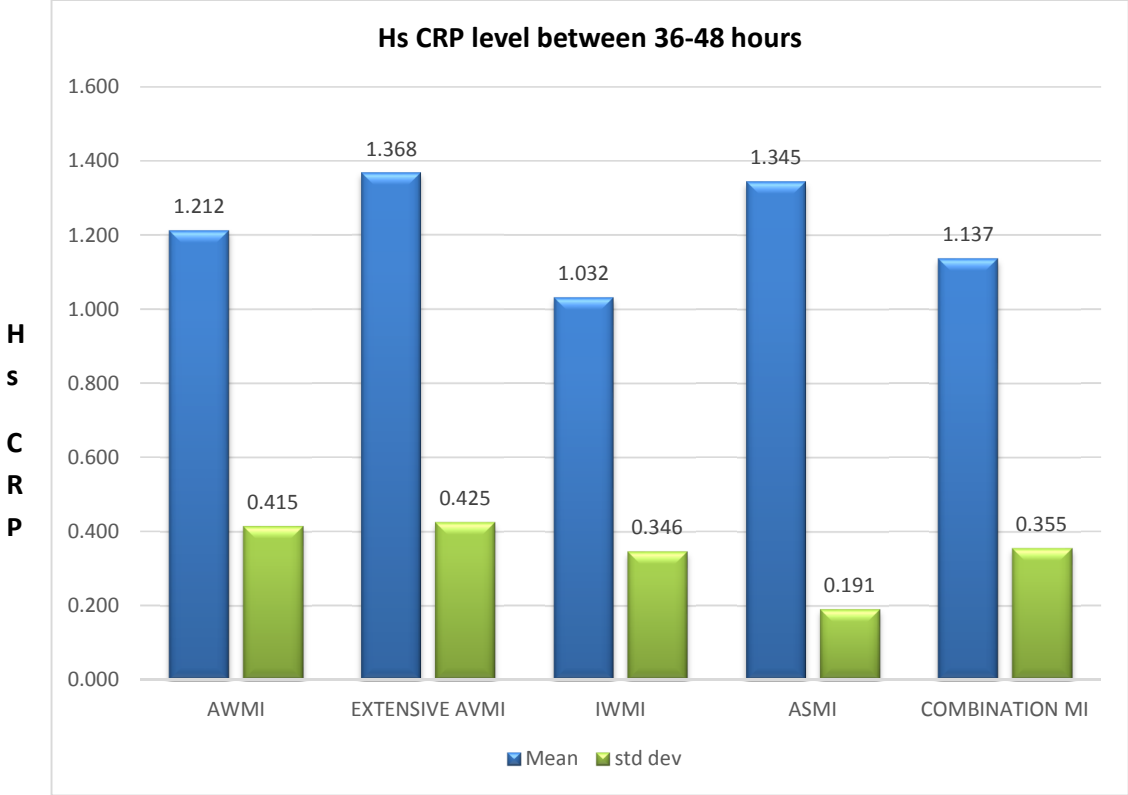
BAR DIAGRAM FOR BASELINE VALUES OF Hs- CRP IN DIFFERENT TYPES OF STEMI



INFERENCE:

The mean of baseline values of Hs-CRP for anterior wall myocardial infarction (AWMI), extensive AWMI, inferior wall myocardial infarction (IWMI), antero-septal myocardial infarction (ASMI) and combined IWMI/PWMI (posterior wall myocardial infarction) were found to be 0.480 mg/dl, **0.825 mg/dl**, 0.375 mg/dl, 0.685 mg/dl and 0.404 mg/dl, respectively in our study. *So* ***the highest baseline level of Hs-CRP was recorded for patients with extensive AWMI (0.825mg/dl).***

BAR DIAGRAM FOR PEAK VALUES OF Hs- CRP IN DIFFERENT TYPES OF STEMI



INFERENCE:

The mean of peak values of Hs-CRP for anterior wall myocardial infarction (AWMI), extensive AWMI, inferior wall myocardial infarction (IWMI), antero-septal myocardial infarction (ASMI) and combined IWMI/PWMI (posterior wall myocardial infarction) were found to be 1.212 mg/dl, **1.368 mg/dl**, 1.032 mg/dl, 1.345 mg/dl and 1.137 mg/dl, respectively in our study. *So, **the highest level of Hs-CRP was recorded for patients with extensive AWMI.***

Acute coronary syndrome comprises of a spectrum of cardiac disease from unstable angina to non-ST elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI). They have a common pathogenesis involving thrombus formation on an inflamed atherosclerotic plaque.

Myocardial infarction (MI) is defined as a clinical or pathologic event due to myocardial ischemia associated with evidence of injury or necrosis of the myocardium. Criteria are met when there are typical symptoms, along with confirmative evidence like rise and/or fall of cardiac biomarkers, suggestive electrocardiographic (ECG) features, or Echo-cardiographic findings of loss of viable myocardium or abnormal new regional wall motion.

The definition of ACS depends on the specific characteristics of the *triad consisting of clinical presentation, electrocardiographic changes and elevation of biochemical cardiac markers.* Sometimes, ACS may occur in the absence of electrocardiographic changes, where the diagnosis is established by the presence of previous history of coronary artery disease and by elevations in biochemical markers. The most commonly assayed serum biomarkers for diagnosis of MI are Troponin T and Creatine kinase-MB.

In acute coronary syndrome, rupture of plaque occurs because of inflammatory processes in the atherosclerotic tissue.[41,42] But recent researches indicate that CRP may play an active role in atherogenesis also. But this inflammatory process cannot be studied by imaging techniques or by arterial biopsy as it is impractical. Therefore, there is growing interest in determining the prognostic efficacy of several serum biomarkers of inflammation that can be quantified in detecting coronary artery disease.

These inflammatory serum biomarkers include serum amyloid A, Il-6, intercellular adhesion molecule -1 homocysteines, fibrinogen levels, fibrinolytic capacity, apolipoprotein A& B-100, lipoprotein (a) and highly sensitive- Creactive protein (Hs-CRP)[2].

Necrosis of tissue is a highly potent acute phase stimulus and after myocardial infarction a profound CRP response occurs in the circulation. Importantly, CRP is deposited along with activated complement within all the acute myocardial infarcts and confirmed experimental evidence suggests that the rise in C reactive protein not only reveals the extent of cardiac tissue damage but may also significantly contribute to the severity of ischemic myocardial injury.

C reactive protein is a pentameric protein[43,44] which is ring shaped and rises in the blood in response to inflammatory cytokines. This acute phase protein which is of hepatic origin increases with secretion of interleukin 6 by macrophages and T cells and macrophages, in response to acute and chronic inflammatory conditions like bacterial, viral, or fungal infections, rheumatic diseases, malignancies and tissue necrosis. Physiologically; it binds to lysophosphatidylcholine, which is present on the cell surface of dead or dying cells and thus activates the complement system through the C1Q complex. The *CRP* gene is located on the first chromosome (1q21-q23). This pentameric protein consists of two hundred and twenty four amino acids with a monomeric molecular mass of 25106 Da.

Recently, Hs-CRP has become the most extensively studied inflammatory serum biomarker for ACS. Studies have shown that it shows no diurnal variation or variation according to sex. Initially, it was considered that CRP may be a bystander inflammatory biomarker, but recent researches proved it to be a biomarker of risk in both acute coronary syndrome (ACS) and in patients with myocardial ischaemia.[45] Also, several studies have proved Hs-CRP to be a potent predictor of mortality in acute coronary syndrome independently and in combination with Troponin T.

With this background, the present study was conducted on prognostic implication of Hs-CRP in acute coronary syndrome (ACS) patients admitted in ICCU&IMCU of Thanjavur Medical College & Hospital (TMCH).

Totally 48 acute coronary syndrome patients, who fulfilled the inclusion and exclusion criteria were selected for the study. 48 healthy individuals were chosen as controls. Based on the clinical presentation, ECG findings and positivity for the cardiac biomarker- troponinT, the diagnosis of acute coronary syndrome was established. A Cardiac ECHO was also done. Venous blood was withdrawn from ACS patients and the highly sensitive C reactive protein (Hs CRP) was estimated before 6 hours of admission (baseline value) and between 36-48 hours of admission (peak value). The prognosis of our patients was monitored following thrombolysis and our patients were fully interrogated during the 1 week hospital stay.

Out of the 48 acute coronary syndrome patients who participated in our study; 36 patients were diagnosed as ST elevation MI (STEMI) and 12 patients as non ST elevation MI (NSTEMI). Out of 36 STEMI patients; 20 patients were males and 16 patients were females. Out of 12 NSTEMI patients; 6 patients were males and 6 patients were females.

Among male patients with STEMI; 85% of patients had risk factor of smoking, alcohol, Diabetes mellitus or Systemic Hypertension and 15% of patients had no associated risk factor. Among female patients with STEMI; 81% of patients had risk factor of Diabetes mellitus or Systemic Hypertension and 15% of patients had no associated risk factor.

Among male patients with NSTEMI; 83% of patients had risk factor of smoking, alcoholic, Diabetes mellitus or Systemic Hypertension and 17% of patients had no associated risk factor. Among female patients with NSTEMI; 60% of patients had risk factor of Diabetes mellitus or Systemic Hypertension and 40% of patients had no associated risk factor.

In our study, in STEMI cases the mean value of Hs-CRP measured within 6 hours (baseline value) was **0.52 mg/dl** and the mean of peak value measured between 36-48 hours was **1.82 mg/dl.** In NSTEMI cases, the mean value of Hs-CRP measured within 6 hours (baseline value)) and the mean of peak value of Hs-CRP (measured between 36-48 hours) were **0.29 mg/dl and 0.97 mg/dl,** respectively. For the controls, the mean value of Hs-CRP for males was 0.12 mg/dl and for females it was 0.19mg/dl. (Normal range of Hs-CRP <0.2mg/dl)

In *male patients with STEMI*, the mean value of Hs-CRP measured within 6 hours (baseline value) and the mean of peak value of Hs-CRP measured between 36-48 hours were **0.50 mg/dl and 1.03 mg/dl,** respectively**.**

In *female patients with STEMI*, the mean value of Hs-CRP measured within 6 hours (baseline value) and the mean of peak value of Hs-CRP measured between 36-48 hours were **0.55 mg/dl and 1.37 mg/dl,** respectively.

In *male patients with NSTEMI*, the mean value of Hs-CRP measured within 6 hours (baseline value)) and the mean of peak value of Hs-CRP measured between 36-48 hours were **0.33 mg/dl and 0.99 mg/dl,** respectively.

In *female patients with NSTEMI*, the mean value of Hs-CRP measured within 6 hours (baseline value)) and the mean of peak value of Hs-CRP measured between 36-48 hours were **0.24 mg/dl and 0.95 mg/dl,** respectively.

In our study, both baseline and peak values of Hs-CRP were elevated in patients with STEMI and NSTEMI but the ***peak values of Hs-CRP measured between 36-48 hours were significantly elevated.*** This suggests that an inflammatory process is responsible for the pathogenesis

of myocardial infarction. In our study, both baseline and peak levels of CRP were considerably higher in STEMI patients when compared to those of NSTEMI patients.

The mean of peak values of Hs-CRP in males for anterior wall myocardial infarction (AWMI), extensive AWMI, inferior wall myocardial infarction (IWMI), antero-septal myocardial infarction (ASMI) and combined IWMI/PWMI (posterior wall myocardial infarction) were found to be 1.12 mg/dl, **1.29 mg/dl**, 0.94 mg/dl, 0.96 mg/dl and 0.96 mg/dl, respectively in our study. *So,* ***for males the highest level of Hs-CRP was recorded for patients with extensive AWMI (1.29mg/dl).***

In females, the mean of peak value of Hs-CRP with anterior wall myocardial infarction (AWMI), extensive AWMI, inferior wall myocardial infarction (IWMI), antero-septal myocardial infarction ASMI and combined IWMI (inferior wall myocardial infarction)/PWMI (posterior wall myocardial infarction) was found to be 1.38 mg/dl, **1.77 mg/dl**, 1.37 mg/dl, 1.34 mg/dl and 1.20 mg/dl, respectively. ***The highest level of Hs-CRP was recorded for patients with extensive AWMI (1.77mg/dl) among females also.***

Among male patients with STEMI; there was *equal number of cases in positive and negative Troponin T groups*. Among female patients with STEMI; *12% of patients had negative Troponin T and 88 % of patients had positive Troponin T test.*

In this study, we inferred that among 36 STEMI patients; ***12 patients showed a negative result for Troponin T (with window period < 4hours) but had an increased level of Hs-CRP*** with positive ECG findings. Similar observation has been noted by De winter RJ and Morrrow DA in their correlative studies on Hs-CRP and Troponin T.

In our study, ***patients with Hs- CRP level greater than 1mg/dl had a lower Ejection fraction and death occurred among extensive AWMI patients, who had a baseline value of Hs-CRP greater than 1.2mg/dl.*** This inference in our study may suggest *that higher the Hs-CRP recorded in ACS pateints, more severe the myocardial infarction;* lower the ejection fraction and greater the risk of heart failure.

Similar inference has been found in a study conducted by Koc M (2010) to investigate the levels of Hs-CRP and their relationship with the severity of CAD in individuals with stable CAD.[46] The ROC curve analysis revealed different cut-off values of Hs-CRP levels in correlation with the severity of CAD.

Brunetti et al (2006) has also found a similar inference that elevated CRP values during Q wave MI was linked to the extent of damage of the myocardium in his correlative study on C reactive protein in individuals with acute coronary syndrome to clinical diagnosis, extent of damage of the myocardium, ejection fraction and findings in the angiogram.[47]

Among male patients with STEMI; 25% of patients had normal level of SGOT and 75% of patients had elevated levels of SGOT. In female patients with STEMI; 12% of patients had normal level of SGOT and 88% of patients had elevated levels of SGOT. In patients with NSTEMI; 8% of patients had normal level of SGOT and 92% of patients had elevated levels of SGOT.

The American Heart Association and U.S. Centers for Disease Control and Prevention have defined risk groups of ACS as follows: low risk (Hs- CRP <0.1mg/dl), intermediate risk (Hs-CRP 0.10 – 0.30mg/dl) and high risk (Hs-CRP > 0.30mg/dl).

Values greater than 1mg/dl suggests of a very strong acute phase response secondary to cardiac ischemia and value > 0.20 mg/dl is associated with an increased likelihood of developing cardiovascular disease or ischemic events.

In the first trial, the **Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (2013)** evaluated patients who had *persistent elevations of Hs-CRP greater than or equal to 2mg/L* to assess cardiovascular events in patients with stable CAD by comparing with interleukin 1β inbibition.[48]

Griselli M[23] et al (1999) suggested that the peak serum CRP level has strong association to post-infarct mortality and morbidity. In a study conducted by de Beer FC[14] et al in 1982, the serum levels of C-reactive protein and creatine kinase-MB were estimated in definite cases of myocardial infarction, in subjects with spontaneous or exercise-induced angina, in cases undergoing coronary arteriography and in individuals with non-cardiac chest pain. In all patients with infarction; CRP values were increased. A statistically significant correlation was found between the peak value of CRP and CK-MB level. In this study; it was inferred that CRP peaked at about 50 hours from the onset of pain but at that time the CK-MB which peaked after 15 hours from the onset of pain had already reached a normal level. 20 patients, who recovered had decreased CRP levels and had a normal value after 7 days from infarction. In 8 patients with death reported within 10 days of admission to hospital, the level of CRP remained elevated.

Pietilä KO[15] et al (1996) assessed the prognostic efficacy of serum C-reactive protein in patients with acute myocardial infarction. In this study, similar to our study; the highest levels of serum C-reactive protein were found between 48 to 96 hours after the onset of myocardial infarction. The corresponding mean CRP values for patients with occurrence of death within 3, 3-6, 6-12 and 12-24 months were 166, 136, 85 and 74mg, respectively. Among patients in whom sudden cardiac death occurred and in patients, the cause of death was because of a new myocardial infarction or due to non cardiac causes, the corresponding mean serum CRP values were 167, 64 and 48mg. The CRP levels in patients who died because of congestive heart failure and in patients who suffered sudden cardiac death showed a significant difference statistically with p-value < 0.001 from the values of individuals who survived or died because of other systemic causes. But, in this study; the highest recorded serum concentrations of creatine kinase or its MB isoenzyme were not associated with death. So, the conclusion of the study was that elevated serum C-reactive protein level in AMI patients treated with thrombolytic drugs is a predictor of increased mortality rate following 6 months of myocardial infarction and a planned thrombolytic therapy may contribute to the survival benefit of acute myocardial infarction in these patients by reducing the inflammatory reaction.

In a study conducted by Anzai T[17] et al (1997) the serum levels of CRP were estimated 24 hourly in two hundred and twenty patients with a first Q-wave aute myocardial infarction. On multivariate analysis; an increase in the peak CRP level ≥ 20 mg/dL was found to predict cardiac rupture, left ventricular aneurysm and cardiac death at 1 year independently, as the relative risk was calculated to be 4.72,2.11 and 3.44, respectively and the p-value were statistically significant for all the 3 variables. It was concluded that there is an association between cardiac rupture, left ventricular aneurysm and cardiac death after 1 year with elevated serum CRP level which is estimated during early hours of AMI. This suggests that elevated CRP values following AMI may aid in predicting infarct expansion.

In patients with STEMI; 8% of patients had normal EF; 25% of patients had moderate EF; 50% of patients had low EF and 17% of patients had very low EF. In patients with NSTEMI; 9% of patients had normal EF; 83% of patients had moderate EF; 8% of patients had low EF and no patients had very low EF.

The Pearson's correlation was done for statistical analysis to assess the association between Hs-CRP and Ejection fraction. In the present study; the Pearson's correlation coefficient of baseline values of Hs-CRP (< 6hrs) to ejection fraction in STEMI and NSTEMI cases were -0.52 and -0.21.The correlation coefficient of peak values of Hs- CRP (36-48 hrs) to ejection fraction in STEMI and NSTEMI cases were -0.65 and -0.54.

The negative r - value is suggestive of inverse relationship between Hs-CRP and Ejection fraction. In STEMI cases, there was *good correlation with both baseline and peak values of Hs-CRP and Ejection fraction with r-value of -0.52 and - 0.65, respectively.* In NSTEMI cases, there was weak correlation with baseline level of Hs-CRP and Ejection fraction with r value of -0.21 *but there was there was good correlation with peak level of Hs-CRP and ejection fraction with r value of -0.54.*

The correlation between baseline and peak values of Hs-CRP vs ejection fraction in STEMI cases was found to be statistically significant with a p-value of 0.001 and 0.006 (p-value <0.05), respectively.

In a study conducted by Canale ML[49] in 2006, elevated levels of C-reactive protein were principally associated with lower left ventricle ejection fraction and a good correlation was found between the level of

CRP and left ventricle ejection fraction with a significant p-value. The results of this study are in accordance with our study.

But in a study conducted by Brunetti et al (2006) on C-reactive protein in patients with acute coronary syndrome in correlation with clinical diagnosis, damage of myocardium, ejection fraction and findings in the angiogram, no correlation was found between peak concentrations of CRP and ejection fraction.[47]

In our study among NSTEMI cases, the correlation between baseline and peak values of Hs-CRP and ejection fraction was statistically insignificant with p-value of 0.5and 0.07, respectively.

On statistical analysis of correlation between baseline (within 6 hours) and peak values of Hs-CRP (36-48 hours) and BMI in STEMI patients, the Pearson's correlation coefficient(r-value) was found to be 0.1 and 0.3, respectively, suggestive of a *weak correlation between baseline and peak values of Hs-CRP and BMI in STEMI cases*.

The Pearson's correlation coefficient (r-value) of correlation between baseline and peak values of Hs-CRP and BMI in NSTEMI patients was found to be 0.01 and 0.2 respectively. This suggests of a *poor strength of*

correlation between the serum values of Hs-CRP and BMI in NSTEMI patients.

In our study, a statistically very weak correlation was found between Hs-CRP and fasting total cholesterol (FLP-TC) and triglycerides (FLP-TGL) in both STEMI and NSTEMI cases with a r-value of -0.16 and -0.07 for TC and TGL vs baseline and peak values of Hs-CRP for patients with STEMI. For patients with NSTEMI patients; the r-value was -0.04 and -0.13 for FLP-TC and FLP-TGL vs baseline and peak values of Hs-CRP.

In a study conducted by Ridker PM[26] (2000) on C reactive protein and other inflammatory markers in predicting cardiovascular disease among females; it was found that the plasma markers, Hs-CRP and the ratio of total cholesterol to HDL cholesterol independently predicted the cardiovascular risk. Hs-CRP had a calculated relative risk of 1.5 while TC to HDL ratio had a calculated relative risk of 1.4.

In another study conducted by him in 2002 on comparison of C-reactive protein and low-density lipoprotein cholesterol levels[26]in the prediction of first cardiovascular event a *weak correlation was found with a r-value=0.08, similar to our study.* In this study, C-reactive protein and

LDL cholesterol measurements independantly identified different high-risk groups. The study suggested that the C reactive protein level strongly predicts cardiovascular risk than LDL cholesterol level and it is an additive to the prognostic information which is rated by the Framingham risk score.

In another study conducted by him (2000) among 5742 participants on the effectiveness of lovastatin to prevent coronary events in patients with higher baseline ratio of total cholesterol to high-density lipoprotein cholesterol. The inference of the study was that high levels of C-reactive protein are associated with an increased risk of coronary events even when there is absence of hyperlipidemia.

In patients with STEMI; 92% of patients had fair prognosis following thrombolytic therapy and in 8% of patient death occurred inspite of thrombolytic therapy during their hospital stay.In STEMI patients, *the correlation between prognosis and the baseline values of Hs-CRP was found to be statistically significant with a p-value =.001*. In our study, it was not possible to assess the correlation between treatment outcome and the peak values of Hs-CRP among STEMI patients, as peak values of Hs-CRP could not be assessed in patients who died before 36 hours, despite intensive therapy.

The correlation between the prognosis and baseline values of Hs-CRP of patients with extensive AWMI (among STEMI cases) was assessed and it was found to have a statistically significant p-value=.002. This infers that *high baseline values of Hs- CRP in extensive MI are associated with poor prognosis.* The mean of baseline value of Hs-crp in patients who faced death due to extensive AWMI was measured to be 1.33mg/dl.

Based on the results of our study;

- Higher values of baseline and peak values of Hs-CRP were seen in patients who had ST – elevation MI (STEMI) than in Non ST – elevation MI (NSTEMI).

- The patients with higher peak values of Hs-CRP had a poor Ejection fraction and the association between them was statistically significant in our study.

- Patients with higher baseline value of Hs- CRP greater than or equal to 1.3 along with findings of extensive MI in the electrocardiogram and low ejection fraction had poor prognosis.

This suggests that the assessement of Hs-CRP levels may enable the physician in detecting the prognosis of acute coronary syndrome patients and plan a more prompt and effective reperfusion therapy.

A larger sample size could have added the strength of the present study but the uniqueness of our study is that the prognostic implication of HS-CRP in acute coronary syndrome patients has been assessed with a short term follow up (during the 1 week hospital stay of the patients) following thrombolytic therapy as in most of the studies the prognostic implication of HS-CRP has been assessed with a long term follow-up of several months.

Higher level of baseline Hs-CRP along with extensive myocardial infarction in the Electrocardiogram is associated with a poor prognosis.

So, the assessment of Hs-CRP levels may enable the physician in detecting the prognosis of acute coronary syndrome patients and in planning a more prompt and effective reperfusion therapy.

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ANNEXURE -1

STUDY – hs CRP IN MI

Sl. No.

Date:

1. Name :

2. Age :

3. Sex :

4. Address :

5. RISK Factor :

DM	SHT	CKD

SMOKER	ALCOHOLIC

6. B.M.I.

7. BLOOD PRESURE :

8. PULSE RATE :

9. Type of MI :

STEM I	NSTEM I

10. STEM I :

AWMI	ASMI	EXTEN.AWMI	IWMI	IWMI +PWMI	IWMI RVMI PWMI	LATERIL MI

11. WINDOW PERIOD :

12. KILLIP CLASS :

13. TIMI SCORE :

14. TROP – T

POSITIVE	NEGATIVE

15. AST

16. FASTING LIPID PROFILE

TC
TGL

17. H SCRP level

With in 6HRS.	36 - 48 HRS.

18. ECHO :

19. OUT COME During Hospital stay :

ANNEXURE 2A

CONSENT FORM

Name of the participant:

Documentation of the informed consent:

I have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am over 18 years of age and I am exercising my free power of choice, hereby give my consent to be included as a participant in the study of "**A STUDY ON PROGNOSTIC IMPLICATION OF Hs-CRP IN ACUTE CORONARY SYNDROME (ACS) PATIENTS ADMITTED IN THANJAVUR MEDICAL COLLEGE & HOSPITAL (TMCH)**". The nature and purpose of data is for research work. The procedure has been explained to me in detail in the language understandable to me by the investigator. It has been made clear to me that all personal details like name, place, religion, past history etc., will be kept strictly confidential. I permit the result obtained to be also used for academic purpose.

Thanjavur

Date:

Signature of the patient: Investigator Certificate:

I certify that all the elements including the nature, purpose and possible risks of the above study as described in this consent document have been fully explained to the subject.

Name of the Investigator: Signature of the investigator:

Date:

ANNEXURE 2B

PATIENT INFORMATION SHEET:

You are being asked to take part in a research study entitled "**A STUDY ON PROGNOSTIC IMPLICATION OF Hs-CRP IN ACUTE CORONARY SYNDROME (ACS) PATIENTS ADMITTED IN THANJAVUR MEDICAL COLLEGE & HOSPITAL (TMCH)** ".

You will not get any financial benefits from this study, but your participation may help future generations as it might help to reduce the mortality of renal failure in cirrhotic patients.

Confidentiality is guaranteed. Your identity will not be revealed. You will have to sign a informed consent form.

Your participation is completely voluntary. You may refuse to participate in the study or end your participation in the study at any time without penalty or loss of benefits to which you are otherwise entitled. You are free to ask any question during anytime of the study. We will try to answer any query that you may have.

Signature of the investigator Signature of Participant

Date:

ANNEXURE -2C

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TABLE FOR MALE PATIENTS WITH STEMI

Sl. No	AGE Yrs	SEX	RISK FACTOR	BMI	TYPE OF STEMI	WP HRS	TROP - T	SGOT	FLP TC	FLP TGL	Hs CRP (6 hrs)	Hs CRP (36-48 hrs)	EF	OUTCOME
1	66	M	SHT	24.24	AWMI	1	-	103	151	209	0.83	1.09	38	Fair
2	29	M	Smo/alc.	28.5	AWMI	5	+	25	125	114	0.62	1.41	30	fair
3	42	M	SHT/Smo/alc	26.1	AWMI	3	-	91	215	201	0.48	0.98	48	fair
4	54	M	Smo/alc.	20.86	AWMI/IWMI	9	+	40	233	89	0.52	0.97	45	fair
5	46	M	DM/alc.	25.8	ASMI	11	+	66	69	193	0.42	1.51	35	fair
6	60	M	SHT/Smo	27.16	ASMI	2.5	-	62	208	158	0.53	1.10	45	Fair
7	50	M	Smo/alc.	24.69	ASMI	9.5	+	116	183	51	0.38	0.68	60	fair
8	80	M	Alc.	26.15	ASMI/IWMI	3	-	30	205	74	0.57	0.95	45	fair
9	63	M	NIL	30.59	EXT AWMI	6	+	53	205	168	1.21	NIL	20	DEATH
10	75	M	DM/Smo/alc	21.69	EXT.AWMI.	3	-	40	208	108	0.81	1.32	30	fair
11	32	M	SHT/Smo/alc	25.7	EXT.AWMI	2	+	95	152	132	0.32	0.82	40	fair
12	35	M	NIL	28.1	EXT.AWMI	4.5	+	46	198	62	0.3	1.15	38	FAIR
13	42	M	Smo/alc.	23.2	IWMI/PWMI	4	-	62	152	102	0.56	0.79	52	FAIR
14	65	M	SHT/Smo	26.71	IWMI/PWMI	5	+	121	54	160	0.41	0.82	50	FAIR
15	44	M	SHT/Smo/alc	25.70	IWMI/PWMI	5.5	-	63	223	104	0.38	0.69	65	FAIR
16	75	M	DM/SHT	23.21	IWMI/PWMI	3	+	46	168	106	0.52	0.84	52	FAIR
17	53	M	SHT	21.10	IWMI/PWMI/RVMI	4	-	27	208	152	0.4	1.54	20	FAIR
18	54	M	NIL	30.76	IWMI	3	-	56	198	108	0.3	1.01	58	FAIR
19	53	M	Alc	20.08	IWMI	8.5	+	68	167	63	0.3	0.93	58	FAIR
20	54	M	Smoker	23.13	IWMI	3	-	72	254	178	0.2	0.95	45	FAIR

TABLE FOR FEMALE PATIENTS WITH STEMI

Sl. No	AGE [Yrs]	SEX	RISK FACTOR	BMI	TYPE OF STEMI	WP [HRS]	TROP-T	SGOT	FLP-TC	FLP-TGL	Hs CRP 6 hrs	HS CRP 36-48hrs	EF	OUT COME
1	60	F	-	25	EXTENSIVE AWMI	9	+	62	192	148	1.41	-	35	Death
2	55	F	DM	29.68	EXTENSIVE AWMI	8	+	79	184	122	0.7	1.92	25	Fair
3	80	F	-	30.30	EXTENSIVE AWMI	9	+	68	102	172	1.28	-	20	Death
4	63	F	-	27.27	EXTENSIVE AWMI	9.5	+	40	151	113	0.57	1.63	48	Fair
5	60	F	SHT	21.37	ASMI	12	+	52	178	78	0.46	1.21	38	Fair
6	70	F	DM/SHT	23.74	ASMI	6	+	50	145	114	0.91	1.48	38	Fair
7	70	F	DM	31.16	AWMI	5	+	80	278	205	0.21	1.12	42	Fair
8	42	F	DM/SHT	21.94	AWMI	4.5	+	48	152	98	0.37	0.92	50	Fair
9	55	F	DM	24.24	AWMI	3	-	105	168	148	0.48	2.10	30	Fair
10	48	F	DM	23.53	IW/PWMI	12	+	113	182	36	0.29	0.83	55	Fair
11	60	F	SHT	22.64	IW/PWMI	9	+	68	178	98	0.40	1.83	38	Fair
12	67	F	SHT	26.61	IW/PWMI	10	+	24	193	172	0.28	0.89	45	Fair
13	43	F	DM/SHT	22.15	IW/PWMI	10	+	125	223	168	0.31	1.11	35	Fair
14	58	F	SHT	27.19	IW/PWMI/RVMI	3	-	54	96	69	0.46	1.38	38	Fair
15	62	F	DM/SHT	25.97	IWMI	7	+	89	138	68	0.36	1.77	35	Fair
16	54	F	SHT	28.41	IWMI	6	+	62	172	142	0.32	0.98	56	Fair

TABLE FOR MALES & FEMALES PATIENTS WITH NSTEMI

Sl. No	AGE Yrs	SEX	RISK FACTOR	BMI	TYPE OF STEMI	WP [HRS]	TROP T	SGOT	FLP-TC	FLP-TGL	Hs CRP 6 hrs	Hs CRP 36-48hrs	EF	OUTCOME
1	92	M	SHT	18.81	NSTEMI		+	29	185	108	0.31	1.01	40	Fair
2	60	M	SMO	19.67	NSTEMI		+	64	138	77	0.32	0.98	52	Fair
3	52	M	-	27.72	NSTEMI		+	45	162	102	0.46	1.21	48	Fair
4	44	M	DM/SMO	23.12	NSTEMI		+	53	128	162	0.14	0.82	55	Fair
5	56	M	SHT/DM	29.12	NSTEMI		+	62	156	110	0.26	0.91	45	Fair
6	25	M	Alc.	22.26	NSTEMI		+	82	156	50	0.52	1.02	45	Fair
7	65	F	SHT	24.89	NSTEMI		+	62	192	162	0.23	0.81	42	Fair
8	66	F	DM/SHT	28.20	NSTEMI		+	100	168	148	0.25	1.27	34	Fair
9	58	F	DM/SHT	25.20	NSTEMI		+	68	192	162	0.31	1.08	45	Fair
10	47	F	-	23.1	NSTEMI		+	48	152	102	0.12	0.62	52	Fair
11	42	F	SHT	27.1	NSTEMI		+	56	108	162	0.21	0.91	43	Fair
12	34	F	-	29.3	NSTEMI		+	62	72	156	0.36	1.01	40	Fair